SYNTHESIS OF AMINO ACIDS THROUGH IMIDAZOLONES

(A NEW METHOD)

THESIS SUBMITTED TO
THE ALIGARH MUSLIM UNIVERSITY
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G.M.Devasia.

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SUMMARY

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A new method for the synthesis of α-amino acids, involving 2,4-disubstituted 5(4H)-imidazolones as intermediates has been developed. The 2-substituted 5(4H)-imidazolones posses an active methylene group which undergoes aldol type of condensation with carbonyl compounds very readily to give unsaturated 2,4-disubstituted 5(4H)-imidazolones, the nitrogen analogues of unsaturated azlactones. Therefore, on the basis of analogy with azlactone synthesis it was possible to develop imidazolone synthesis of amino acids. The unsaturated 2,4-disubstituted 5(4H)-imidazolones obtained were quite stable compounds which could be reduced to the saturated imidazolones in high yields by catalytic hydrogenation. The saturated imidazolones were then successfully hydrolysed to the corresponding acylamino acid amides, acylamino acids and amino acids under different conditions.

For the imidazolone synthesis to be used as a general method for the synthesis of amino acids it was considered necessary to study the intermediate steps and to work out optimum conditions for carrying out various stages of the synthesis in high yields and also to examine their scope and limitations. In view of this, studies were carried out for the synthesis of unsaturated 2,4-disubstituted 5(4H)-imidazolones, their reduction to the saturated

imidazolones and hydrolysis of the saturated imidazolones, under different conditions, to amino acids and their derivatives. The results of these studies were encouraging enough to suggest the imidazolone synthesis of amino acid as a general method similar to the azlactone synthesis with which it compares quite favourably.

Method for the synthesis of unsaturated 2,4-disubstituted 5(4H)-imidazolones by condensing carbonyl compounds with 2-substituted 5(4H)-imidazolones was improved so that aldehydes were condensed with a mixture of glycine ester and an imidic acid ester when the unsaturated imidazolones were obtained in very high yields. Further, a more convenient synthesis of unsaturated imidazolones was developed by the condensation of carbonyl compounds with a mixture of glycine ester and an imidic acid ester hydrochlorides in the presence of sodium bicarbonate without involving isolation of free esters. The unsaturated imidazolones prepared were 2-phenyl-4-benzylidene-5(4H)-imidazolone (76.3 %), 2-phenyl-4-(p-hydroxybenzylidene)-5(4H)-imidazolone (85.6%), 2-phenyl-4-anisylidene-5(4H)-imidazolone (85.2%), 2-phenyl-4-(3,4-dimethoxybenzylidene)-5(4H)-imidazolone (87.8%), 2-phenyl-4-isobutylidene-5(4H)-imidazolone (55.6%), 2-benzyl-4-benzylidene-5(4H)-imidazolone (46.4%), 2-benzyl-4-anisylidene-5(4H)-imidazolone (48.7%), 2-methyl-4-benzylidene-5(4H)-imidazolone (28.1%) and 2-methyl-4-anisylidene-5(4H)-imidazolone (57.3%). 2-Phenyl-4-(p-hydroxy-

benzylidene)-5(4H)-imidazolone, 2-benzyl-4-anisylidene-5(4H)-imidazolone and 2-methyl-4-anisylidene-5(4H)-imidazolone are new compounds.

A number of unsaturated imidazolones were hydrogenated to saturated imidazolones in high yields (60-87%) using palladium on strontium carbonate and platinum oxide catalysts in the presence of ethyl acetate as solvent. Thus 2-phenyl-4-benzyl-5(4H)-imidazolone (84.1%), 2-phenyl-4-(p-hydroxybenzyl)-5(4H)-imidazolone (86.8%), 2-phenyl-4-anisyl-5(4H)-imidazolone (82.4%), 2-phenyl-4-sec-butyl-5(4H)-imidazolone (71.9%), 2-phenyl-4-isopropyl-5(4H)-imidazolone (74.3%), 2,4-dibenzyl-5(4H)-imidazolone (59.5%) and 2-benzyl-4-anisyl-5(4H)-imidazolone (64.6%) were prepared. All these saturated imidazolones except 2-phenyl-4-benzyl-5(4H)-imidazolone are new compounds.

Saturated 2,4-disubstituted 5(4H)-imidazolones were hydrolysed to acylamino acid amides by heating with sodium hydroxide solution. Benzoylphenylalanine amide (26.6%), benzoylisoleucine amide (68.3%), benzoylvaline amide (45.8%) and phenylacetylphenylalanine amide (29.3%) were prepared by this method. Benzoylisoleucine amide and benzoylvaline amide are new compounds.

Saturated 2,4-disubstituted 5(4H)-imidazolones were hydrolysed to acylamino acids by prolonged heating with

sodium hydroxide solution. Benzoylphenylalanine (68.5%), N-benzoyltyrosine (19.4%), benzoyl-O-methyltyrosine (47.8%), phenylacetylphenylalanine (74.9%) and phenylacetyl-O-methyltyrosine (69.8%) were prepared by this method. Phenylacetyl-O-methyltyrosine is a new compound.

Saturated 2,4-disubstituted 5(4H)-imidazolones were hydrolysed with barium hydroxide to amino acids. The amino acids thus prepared were phenylalanine (67.9%), O-methyltyrosine (58.9%) and valine (31.9%).

A REVIEW OF THE METHODS USED IN THE SYNTHESIS OF α-AMINO ACIDS

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α-Amino acids are the constituents of proteins and therefore they are required for nutrition and for the synthesis of polypeptides. With increasing research activities in these fields and possible use of "essential" amino acids as dietary supplements for the enrichment of food, synthetic amino acids are in increasingly greater demand. There are a number of methods for the synthesis of amino acids with different scope and limitations so that some amino acids can be synthesised better by one method than by the others and therefore the use of a variety of methods may ultimately be expected to lead to the synthesis of all the amino acids in large quantities. The following is a critical review of the various methods used in the synthesis of amino acids which would provide the proper context in which scope and limitations of the imidazolone synthesis of amino acids can be fully examined.

I: α-HALOGEN ACID METHODS

(a) Direct amination with aqueous or liquid ammonia.

(1) From monocarboxylic acids.

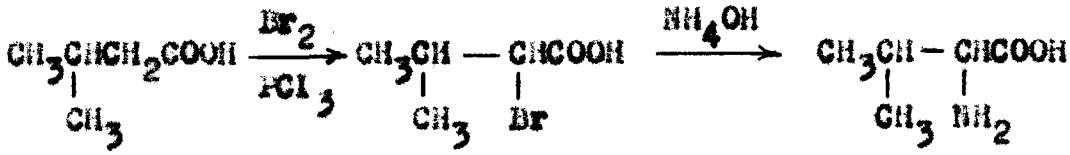
Glycine: The synthesis of glycine from chloroacetic acid and ammonia was originated by Cahours (1) in 1858 and confirmed by Perkin and Duppa (2). It has been improved much by a number of investigators (3-10) and now it may be considered to be the best method for the synthesis of glycine. According to the modification of Tobie and Ayres (8) 75-77% yield of pure glycine was obtained. The

$$\begin{array}{l} CH_2COOH \\ | \\ Cl \end{array} \text{ (0.5 mole) } + NH_4OH \text{ (30 moles)} \longrightarrow \begin{array}{l} CH_2COOH \\ | \\ NH_2 \end{array}$$

large excess of ammonia was used to minimize the formation of diglycolamic and triglycolamic acids.

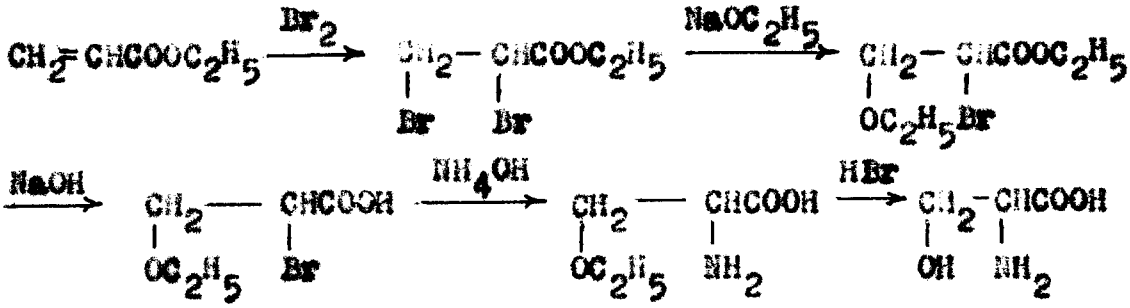
Alanine, valine, norleucine, leucine etc. In the preparation of other amino acids the corresponding α-bromo acids are usually used. Tobie and Ayres (11) obtained 70-80% yield of alanine when α-bromopropionic acid was aminated with a large excess of ammonia. The corresponding chloro acid afforded only 46-60% yield of alanine. Marvel (12) prepared dl-valine in 42% over-all yield according to the following scheme which is essentially the same as described by Clark and Fittig (13) Schlebusch (14) Schmidt and Sachtleben (15)

and Slimmer (16).



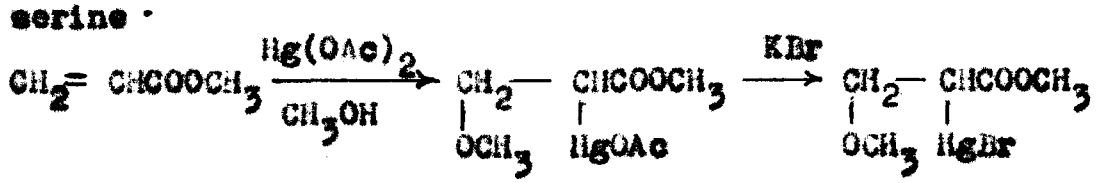
Norleucine (17-19) and leucine (20) were also successfully synthesised similarly, starting from n-caproic and isocaproic acids respectively. Phenylalanine (21) aspartic acid (22-25) and isoleucine (26) have also been made by this general reaction.

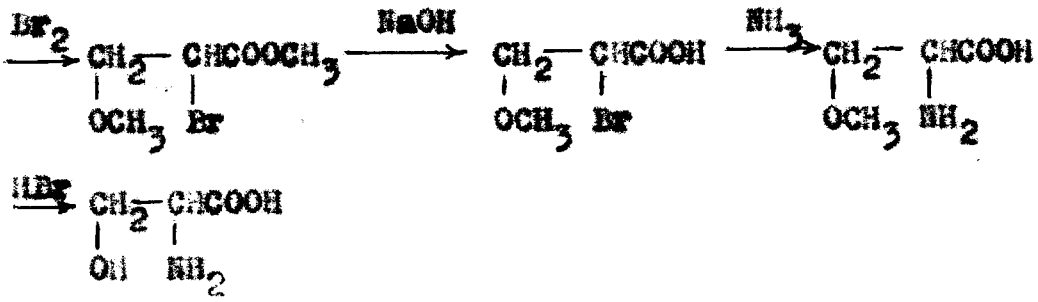
Serine and threonine. Wood and du Vigneaud (27) accomplished the synthesis of serine in 39 % over-all yield as follows:



A mixture of threonine and allo-threonine (mainly the latter) was similarly prepared by Carter and Ney (28) from ethyl crotonate.

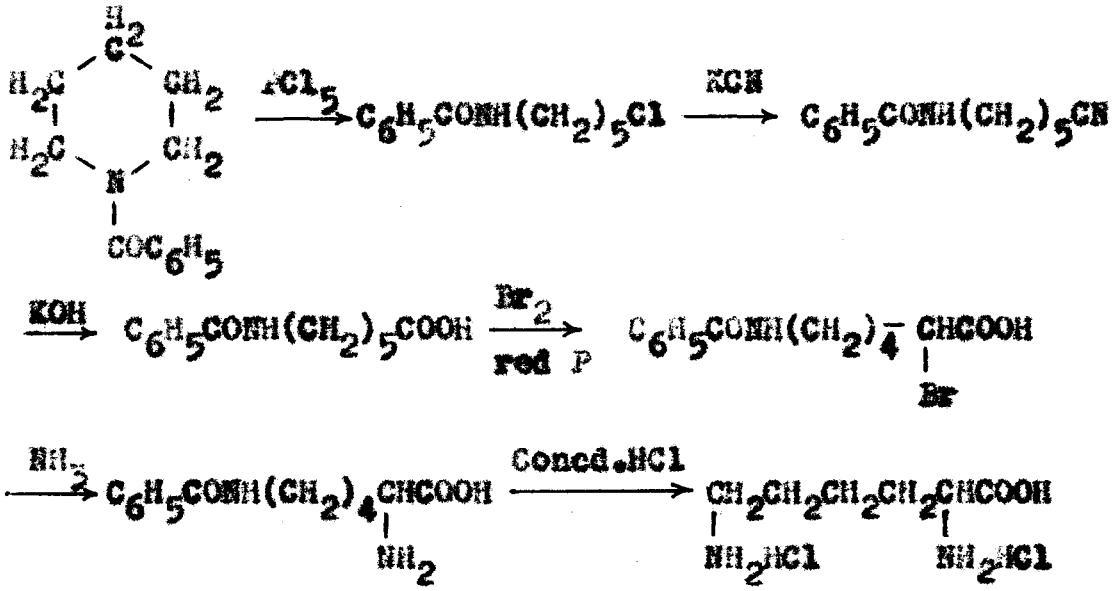
Carter and West (29) synthesised serine in 30-40 % yield according to the following scheme which is a modification of Schiltz and Carter (30) method for the synthesis serine.



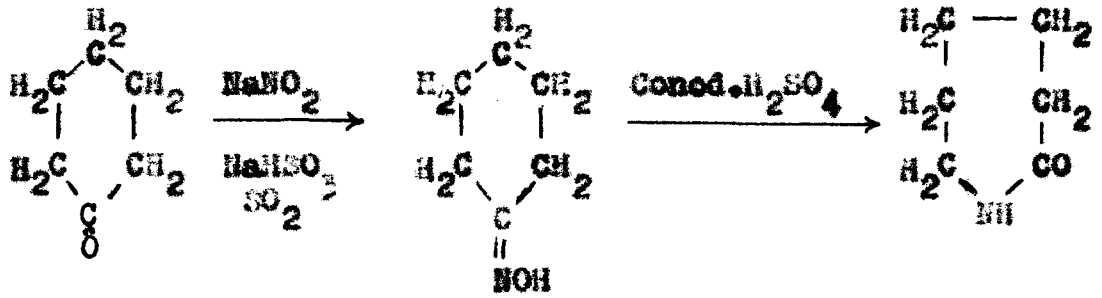


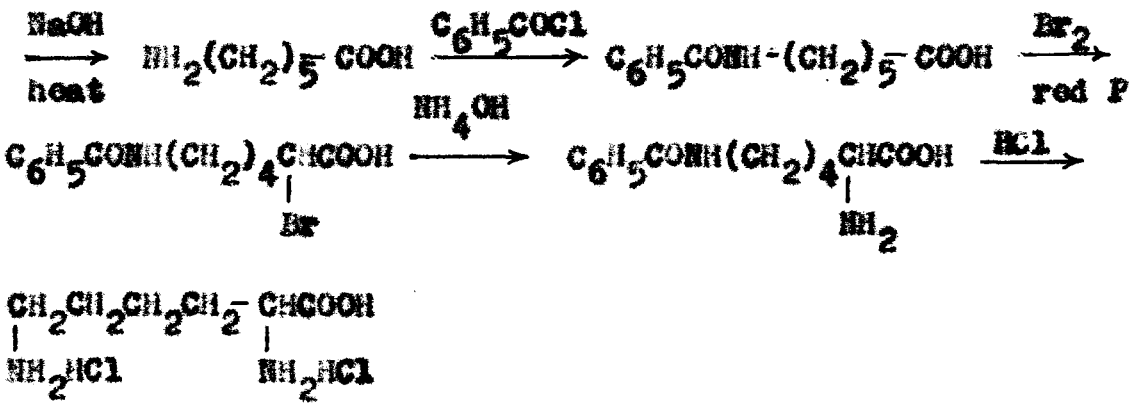
Threonine was prepared in a similar manner by Abderhalden and Heyns (31) and Carter and West (32) starting from crotonic ester and crotonic acid respectively.

Lysine, proline and other amino acids: V.Braun (33) synthesised lysine from benzoylpiperidine as follows:



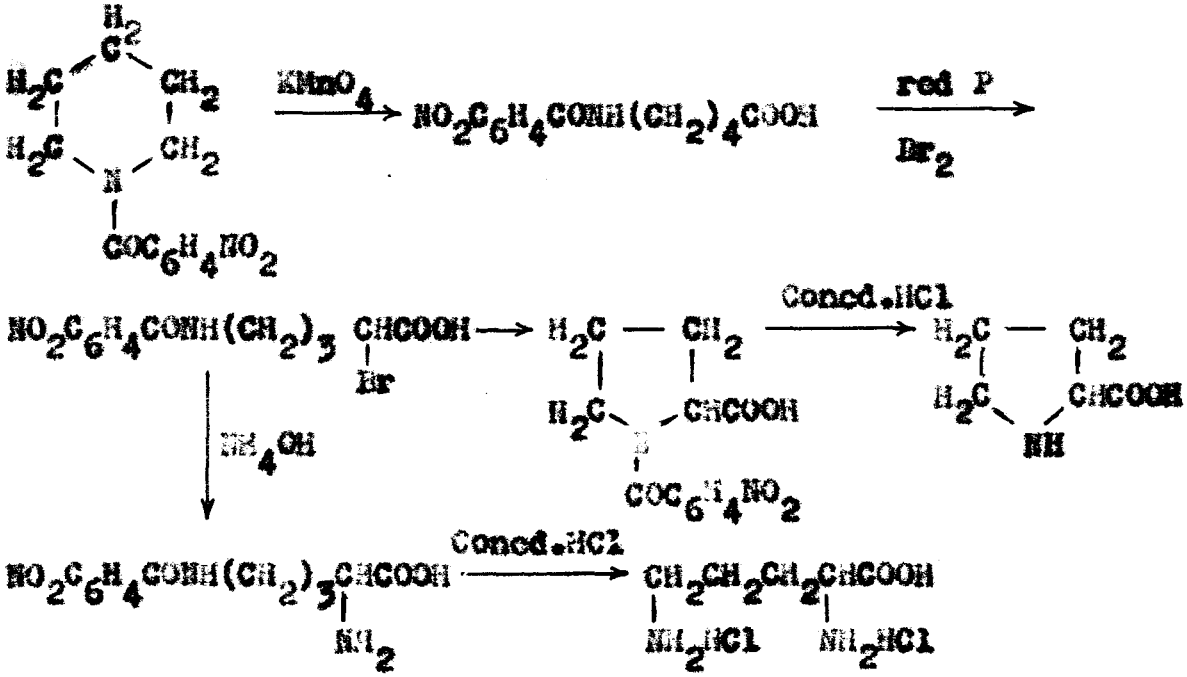
Lysine was prepared by Eck and Marvel (34) starting with cyclohexanone by the following reactions:





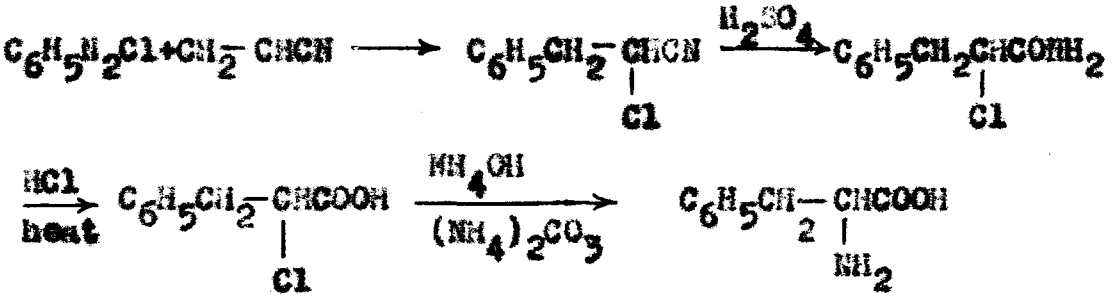
In 1947 Galat (35,36) and in 1953 Odo and Himizu (37) improved Fox-Marvel method for the synthesis of lysine. Schniepp and Marvel (38) synthesised ornithine and arginine starting with cyclopentanone through the oxime by a somewhat similar method.

Fischer and Zemplen (39) accomplished the syntheses of ornithine and proline according to the following scheme:



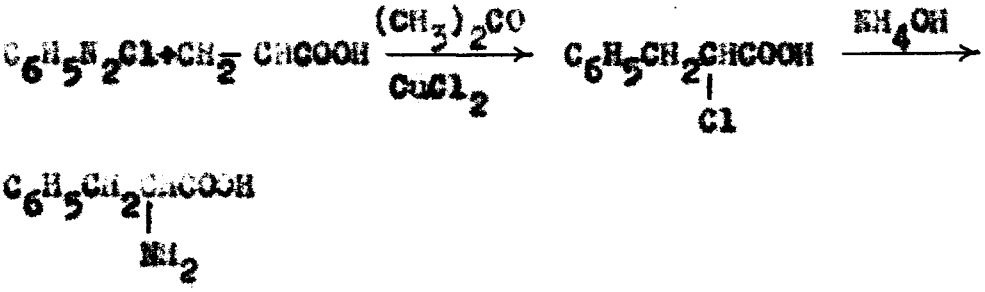
The synthesis of proline was carried out also by Dunn (40) starting with cyclopentanone.

Phenylalanine and tyrosine. Gaudry (41,42) has synthesised phenylalanine from the easily available benzenediazonium chloride and acrylonitrile as follows:



Tyrosine was similarly prepared.

In 1960 Filler and Novar (43) used acrylic acid instead of acrylonitrile in the above syntheses. Thus phenylalanine was prepared according to the following reactions:



(ii) From substituted malonic acids

Direct halogenation of malonic acids proceeds much more smoothly than that of the corresponding monocarboxylic acids. Therefore advantages has been taken of substituted malonic acids in the syntheses of ∝-amino acids.

Phenylalanine, leucine, isoleucine,norleucine and valine. Isoleucine was synthesised by a number of investigators (44-46) by the bromination of secondary butylmalonic acid followed by decarboxylation and amination. Emil Fischer (47) prepared phenylalanine and he and Schmitz (48) prepared leucine similarly. Marvel and co-workers (49-52) improved this general method after hard labour for the practical preparations of valine, isoleucine, norleucine and phenylalanine and now it can be considered as one of the best methods for the syntheses of these amino acids when they are required in large quantities. Thus phenylalanine was prepared as follows in 60 % yield based on diethyl benzylmalonate.

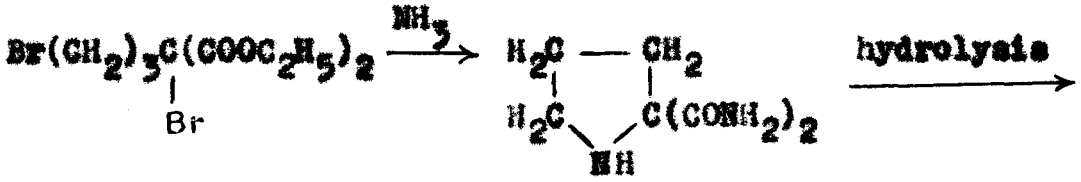
$$C_6H_5CH_2Cl + CH_2(COOC_2H_5)_2 \xrightarrow[C_2H_5OH]{Na} C_6H_5CH_2CH(COOC_2H_5)_2 \xrightarrow{KOH}$$

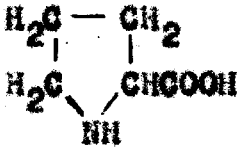
$$C_6H_5CH_2CH(COOH)_2 \xrightarrow{Br_2} C_6H_5CH_2\underset{\displaystyle Br}{\underset{|}{C}}(COOH)_2 \xrightarrow{heat}$$

$$C_6H_5CH_2\underset{\displaystyle Br}{\underset{|}{C}}HCOOH \xrightarrow{NH_4OH} C_6H_5CH_2\underset{\displaystyle NH_2}{\underset{|}{C}}HCOOH$$

Proline, hydroxyproline and histidine. Willstatter (53-55) in 1903 synthesised proline from trimethylene bromide and sodiomalonic ester as follows:

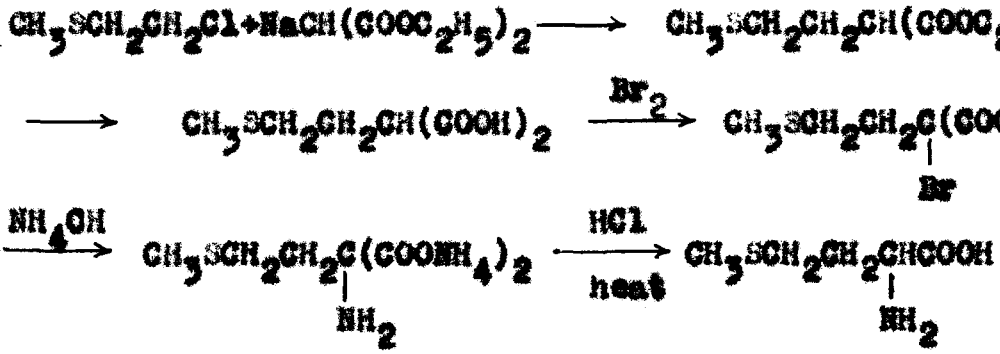
$$BrCH_2CH_2CH_2Br + NaCH(COOC_2H_5)_2 \longrightarrow Br(CH_2)_3CH(COOC_2H_5)_2 \xrightarrow{Br_2}$$





Leuchs and Brewster (56-58) prepared hydroxyproline from δ-chloro-γ-valerolactone-α-carboxylic acid which had been prepared from sodiomalonic ester and epichlorohydrin by Traube and Lehmann (59). Pymann (60) accomplished the synthesis of histidine starting with 4-chloromethyl imidazolene and sodiomalonic ester.

Methionine. Windus and Marvel (61) used sodiomalonic ester in the synthesis of methionine.

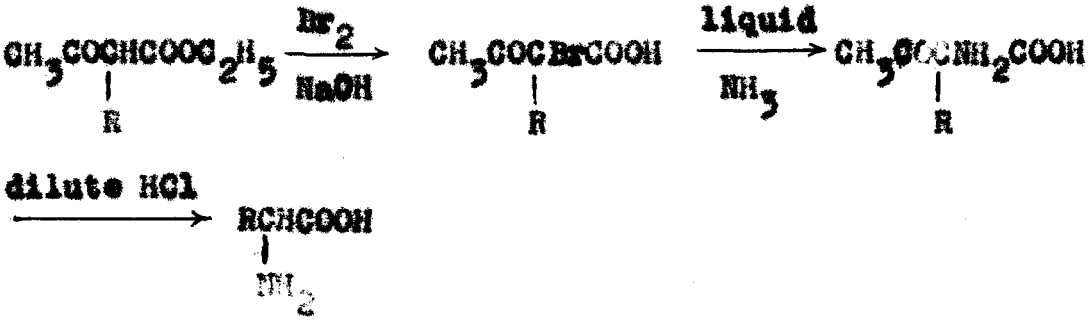


Methionine was prepared also by Patterson and du Vigneaud (62) in 1935 and Hill and Robson (63) in 1936.

(iii) From substituted acetoacetic esters.

Takizawa (64,65) synthesised norleucine, leucine, alanine, valine, phenylalanine, aspartic acid and glutamic

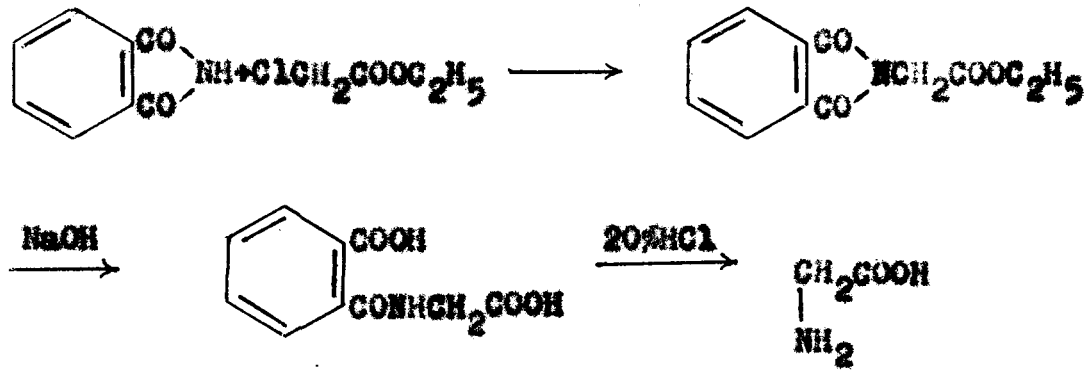
acid in 36-60% yields starting with appropriate alkylaceto-acetic esters.



(b) Amination with phthalimide, sulphonamide and hexamethylene-tetramine.

(1) Gabriel phthalimide method

In 1888 Goedeckmeyer (66) used potassium phthalimide in the synthesis of glycine from chloroacetic ester. In the following year Gabriel and Kroseberg (67) improved this method for the large scale preparation of glycine.



In 1955 Paris and coworkers (68) prepared glutamic acid using this method.

In 1939 Schoenheimer and Ratner (69) employed Gabriel phthalimide method in the syntheses of glycine, deutroleucine and lysine containing isotopic nitrogen.

(ii) Sulphonamide method.

Schroeter (70,71) synthesised glycine and alanine from chloroacetic acid and α-bromopropionic acid respectively using p-toluenesulphonamide.

$$p\text{-}CH_3C_6H_4SO_2NH_2 + ClCH_2COOH \xrightarrow{NaOH} p\text{-}CH_3C_6H_4SO_2NHCH_2COOH$$

$$\xrightarrow[ClCH_2COCl]{CH_3COCl} \underset{\underset{NH_2}{|}}{CH_2COOH} + p\text{-}CH_3C_6H_4SO_2Cl$$

(iii) Hexamethylenetetramine method.

In 1948 Hillmann and Hillmann (72) prepared glycine, alanine, valine, norleucine, leucine and phenylalanine in excellent yields by treating chloroacetic acid and other appropriate α-bromocarboxylic acids with hexamethylene-tetramine in dioxane or dioxane-xylene mixture and decomposing the addition products obtained with aqueous or alcoholic hydrogen chloride.

II: α-AMINONITRILE AND RELATED METHODS:

(a) Strecker synthesis

α-Aminonitrile was first used by A. Strecker (73) in 1850 in the synthesis of alanine. Therefore this method is often known as Strecker method. Strecker obtained the aminonitrile from aldehyde-ammonia. Later, other workers prepared α-aminonitriles from aldehyde cyanhydrins and also directly from aldehydes.

(i) From aldehyde-ammonias

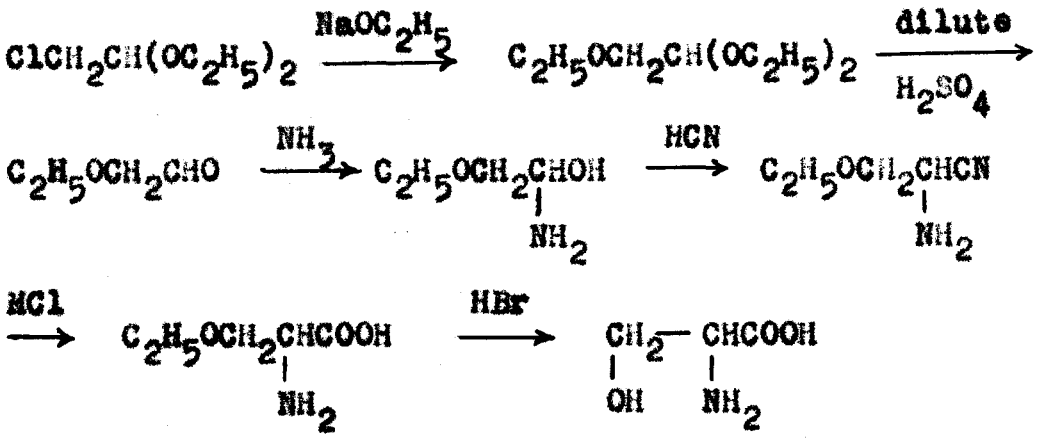
Strecker (73) prepared alanine from acetaldehyde-ammonia as follows:

$$CH_3CHO + NH_3 \longrightarrow CH_3CH(NH_2)OH \xrightarrow{HCN} CH_3CH(NH_2)CN \xrightarrow{HCl}$$

$$CH_3CH(NH_2HCl)COOH \xrightarrow{Pb(OH)_2} CH_3CH(NH_2)COOH$$

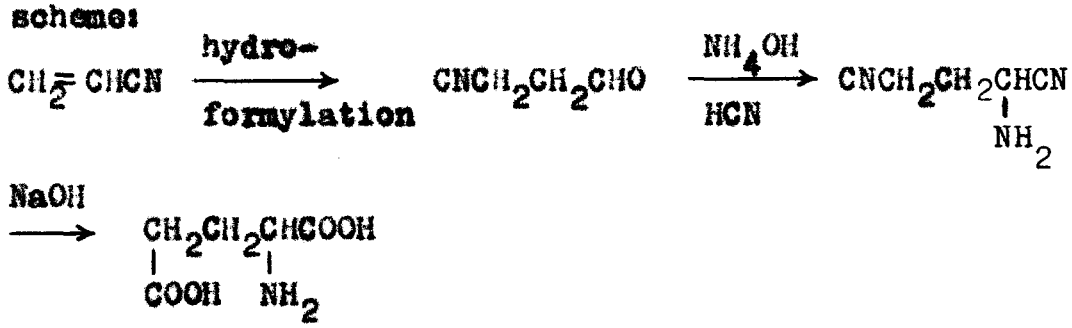
This was the first synthetic preparation of an amino acid. In 1931 Cocker and Lapworth (74) obtained 71.8% yield of alanine from acetaldehyde-ammonia by an improvement of Strecker method.

Leucine (75) valine (76) and serine (77) were synthesised from the appropriate aldelhyde-ammonias by Strecker's original method. In 1906 Leuchs and Geiger (78) synthesised serine according to the following scheme:



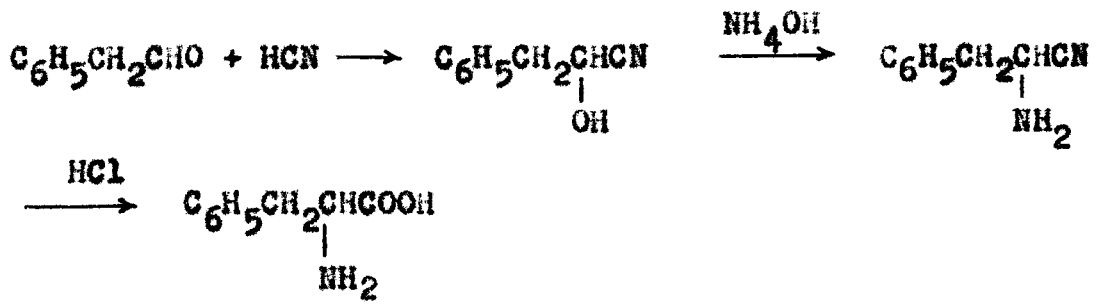
In 1934 Dunn, Redemann and Smith (79) and later Redemann and Icke (80) improved much the above synthesis of serine.

In 1960 Yoshida and coworkers (81) prepared glutamic acid starting from acrylonitrile according to the following scheme:



(ii) <u>From aldehyde cyanhydrins</u>

In 1883 Erlenmeyer and Lipp (82) prepared phenylalanine from phenylacetaldehyde cyanhydrin as follows:



Isoleucine was prepared by Ehrlisch (83) from β-methyl-n-butyraldehyde cyanhydrin. In 1925 Keimatsu and Sugasawa(84) synthesised glutamic acid from acrolein according to the following scheme:

$$CH_2{=}CHCHO + C_2H_5OH + HCl \longrightarrow \underset{\displaystyle Cl}{\overset{\displaystyle |}{CH_2CH_2CH}}\,(OC_2H_5)_2 \xrightarrow{KCN}$$

$$\underset{\displaystyle CN}{\overset{\displaystyle |}{CH_2CH_2CH}}(OC_2H_5)_2 \xrightarrow{NaOH} (C_2H_5O)_2CHCH_2CH_2COOH \xrightarrow[H_2SO_4]{\text{dilute}}$$

$$CHOCH_2CH_2COOH \xrightarrow{HCN} HOOCCH_2CH_2\underset{\displaystyle OH}{\overset{\displaystyle |}{C}}HCN \xrightarrow{NH_3} HOOCCH_2CH_2\underset{\displaystyle NH_2}{\overset{\displaystyle |}{C}}HCN$$

$$\xrightarrow{H_2SO_4} HOOCCH_2CH_2\underset{\displaystyle NH_2}{\overset{\displaystyle |}{C}}HCOOH$$

In 1946 Gaudry (85) obtained a very good yield of valine from isobutyraldehyde cyanhydrin. Gluud and Klempt (86) in 1950 synthesised glycine in excellent yield according to the following scheme:

$$HCHO + HCN \xrightarrow[30\text{–}40^\circ]{pH\ 4.5} HOCH_2CN \xrightarrow[\text{liquid } NH_3, 45^\circ]{\text{large excess of}} \underset{\displaystyle NH_2}{\overset{\displaystyle |}{CH_2CN}}$$

$$\xrightarrow{Ba(OH)_2} \underset{\displaystyle NH_2}{\overset{\displaystyle |}{CH_2COOH}}$$

In the same year Gresham and Schweitzer (87) prepared glycine, valine, isoleucine, leucine and glutamic acid in high yields by this method.

(iii) From aldehydes

Aldehydes directly afford α-amino nitriles on treating them with ammonium cyanide (or a mixture of ammonium hydroxide and hydrogen cyanide) or a mixture of alkali cyanide and ammonium chloride. In 1881 Lubavin (88) prepared alanine starting with acetaldehyde and ammonium cyanide as follows:

$$CH_3CHO + NH_4CN \longrightarrow CH_3\underset{\underset{NH_2}{|}}{C}HCN \xrightarrow{HCl} CH_3\underset{\underset{NH_2}{|}}{C}HCOOH$$

Many investigators (89-92) improved this synthesis of alanine from acetaldehyde. Thus Kendall and McKenzie (92) in 1929 synthesised alanine in 52-60 % yield starting with acetaldehyde, ammonium chloride and sodium cyanide.

Other amino acids prepared by this method are leucine (88), methionine (93), valine (85) and glutamic acid (94).

Formaldehyde affords methyleneaminoacetonitrile instead of aminoacetonitrile when treated with a mixture of ammonium chloride and potassium cyanide. Methyleneamino-acetonitrile was thus first prepared in 35% yield by Jay and Curtius (95) in 1894. They obtained very good yield of glycine ester hydrochloride from it on boiling with alcoholic hydrogen chloride. When methyleneaminoacetonitrile was hydrolysed with aqueous hydrogen chloride, glycine hydro-chloride was formed along with ammonium chloride and their separation was difficult.

1. $2CH_2O + KCN + NH_4Cl \xrightarrow{CH_3COOH} CH_2{=}NCH_2CN$

2. $CH_2{=}NCH_2CN \xrightarrow[HCl]{\text{Alcoholic}} \begin{matrix} CH_2COOC_2H_5 \\ | \\ NH_2HCl \end{matrix}$

3. $CH_2{=}NCH_2CN \xrightarrow[HCl]{\text{aqueous}} \begin{matrix} CH_2COOH \\ | \\ NH_2HCl \end{matrix}$

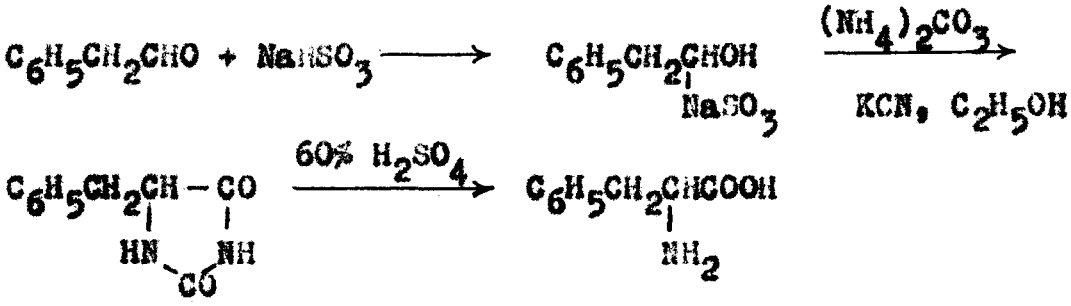
This preparation of methyleneaminoacetonitrile and its conversion to glycine ester hydrochloride and glycine were improved by a number of investigators (74,96-106). Thus Klages (96) in 1903 prepared methyleneaminoacetonitrile in 60% yield and converted into glycine ester hydrochloride in 90 % yield. He also obtained 91% yield of aminoacetonitrile hydrogen sulphate on treating methyleneaminoacetonitrile with warm alcoholic sulphuric acid. Adams and Langely (103) further improved the yield of methyleneaminoacetonitrile to 61-71%. Anslow and King (101,104) obtained practically quantitative yield of glycine on hydrolysing aminoacetonitrile hydrogen sulphate with barium hydroxide.

$$CH_2{=}NCH_2CN \xrightarrow[H_2SO_4]{\text{alcoholic}} \begin{matrix} CH_2CN \\ | \\ NH_2H_2SO_4 \end{matrix} \xrightarrow{Ba(OH)_2} \begin{matrix} CH_2COOH \\ | \\ NH_2 \end{matrix}$$

(b) <u>Bucherer method</u>

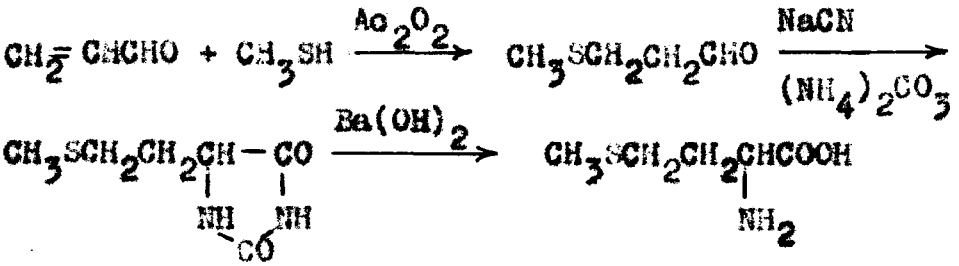
The hydantoins obtained from aldehydes on heating with a mixture of alkali cyanide and ammonium carbonate afford

amino acids on hydrolysis. The first amino acid thus prepared was phenylalanine and this synthesis was carried out by Buchcrer and Lieb (107) in 1934.



Gaudry (85,108) prepared 5-isopropylhydrantoin, 5-methyl-hydantoin and 5-benzylhydantoin using appropriate aldehydes and hydrolysed them with barium hydroxide to valine, alanine and phenylalanine respectively.

In 1950 Livak et al.(109) obtained very high yields of tryptophan, methionine, and valine on hydrolysis of the corresponding hydantoins with barium hydroxide in autoclave. In the next year they prepared (110,111) isoleucine and methionine by hydantoin method. Their synthesis of methionine was according to the following scheme starting from acrolein.



In 1951 White (112) prepared tryptophan, methionine, isoleucine, leucine and alanine by hydrolysing the

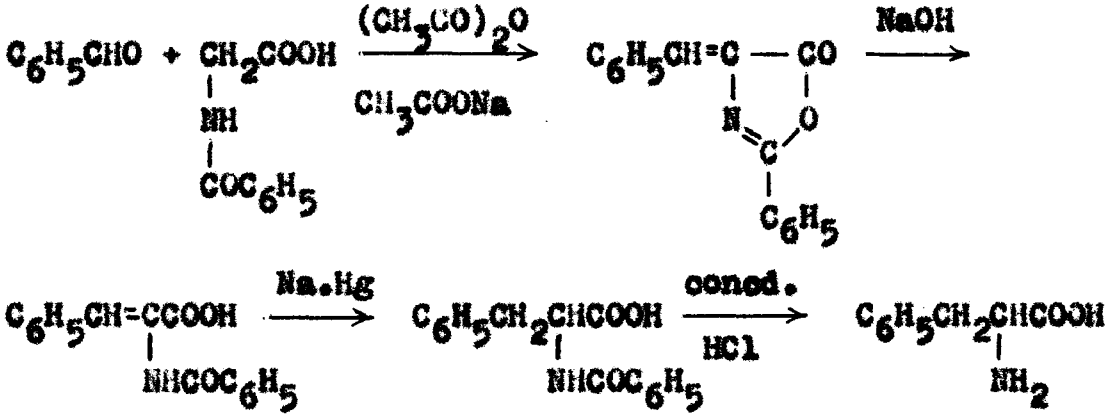
corresponding hydantoins with 3.2 molecular proportions of sodium hydroxide in autoclave. After two years he (113-115) accomplished the syntheses of glycine, alanine, valine, norvaline and tryptophan by the hydrolysis of the hydantoins prepared from appropriate aldehydes by heating with ammonium carbonate and sodium cyanide. The hydantoins were hydrolysed in autoclave with two moles of alkali metal base.

Scott and Rogers (116) Rogers (117) Gaudry (118) and Pollack (119) synthesised lysine employing Bucherer method. Anatol (120) Susuki and Morita (94) and Hori (121) used this method for the synthesis of glutamic acid. In 1955 Grudzinski and Kotelko (122) synthesised methionine by this method.

III: ALDEHYDE CONDENSATION METHODS

(a) Azlactone synthesis

In 1883 Plochl (123) obtained the so called azlactone on condensation of benzaldehyde with hippuric acid in presence of acetic anhydride. After ten years Erlenmeyer (124) improved much this synthesis of azlactone and converted it into phenylalanine according to the following scheme:



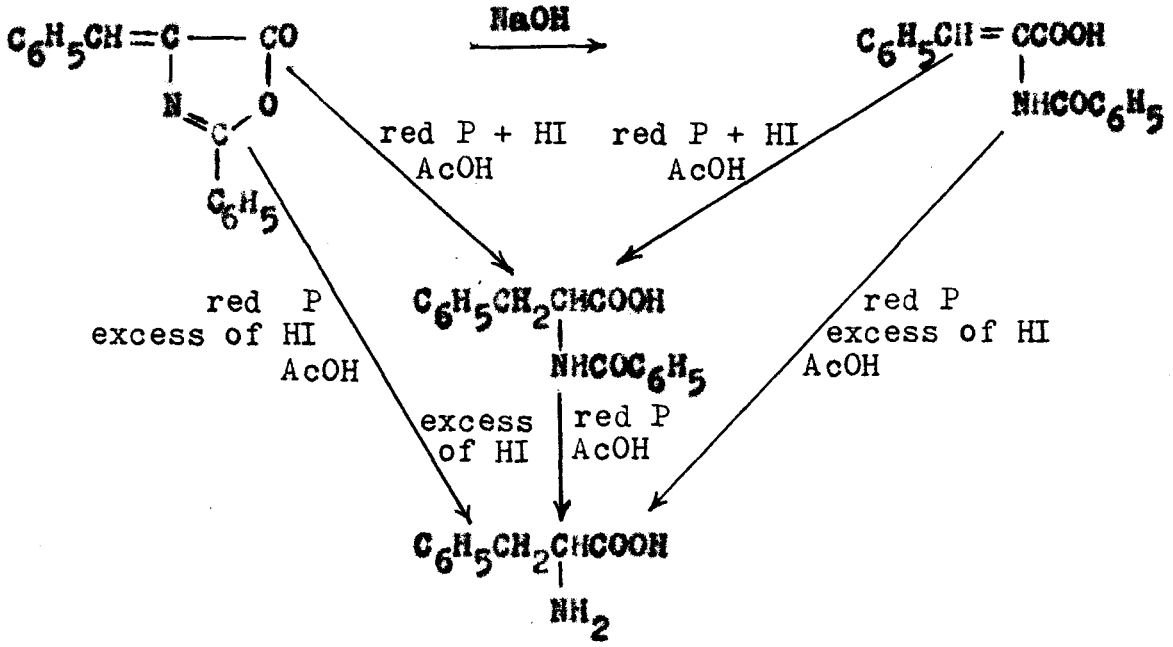
Erlenmeyer (125-127) prepared tyrosine and leucine also by this method. In the syntheses of phenylalanine and tyrosine the yields were excellent except in the third stage. Fischer (128,129) improved this stage and obtained 80% yield of benzoylphenylalanine and 65-70% yield of benzoyltyrosine. Ellingar and Flamand (130,131) in their synthesis of tryptophan by this method used sodium amalgam and absolute alcohol instead of water for the reduction of the acrylic acid and the benzoyltryptophan thus obtained was hydrolysed with sodium hydroxide. Pyman (132) in the synthesis of

histidine hydrolysed its benzoyl derivative with sixty times its weight of 20% hydrochloric acid.

Harington and Barger (133) in their synthesis of thyroxine used hydroiodic acid and red phosphorous for the reduction of the acrylic acid and obtained 3,5-diiodothyronine in 25% yield. Later, Harington and McCartney (134) obtained 82% yield of 3,5-diiodothyronine when a mixture of hydroiodic acid and acetic anhydride was used in the presence of red phosphorous. They (134) prepared phenylalanine and tyrosine also, using this reagent from the corresponding α-benzoylaminoacrylic acids or esters. Hoffmann-LaRoche (135,136) prepared in satisfactory yield 3,5-diiodothyronine directly from the oxazolone employing this reagent. Similarly Gillespie and Snyder (137) obtained 63.67% yield of phenylalanine from the azlactone of α-benzoylaminocinnamic acid.

Thus Harington and Barger reduced Erlenmeyer's original method for the synthesis of α-amino acids to a three stage process and Hoffmann-La Roche to a two stage process. Although these modifications were highly successful in the preparation of inactive α-amino acids they could not afford benzoylamino acids which are useful in the resolution. But in 1931 Lamb and Robson (138) prepared the benzoyl derivatives of phenylalanine and tyrosine both from the corresponding acrylic acids and from the azlactones

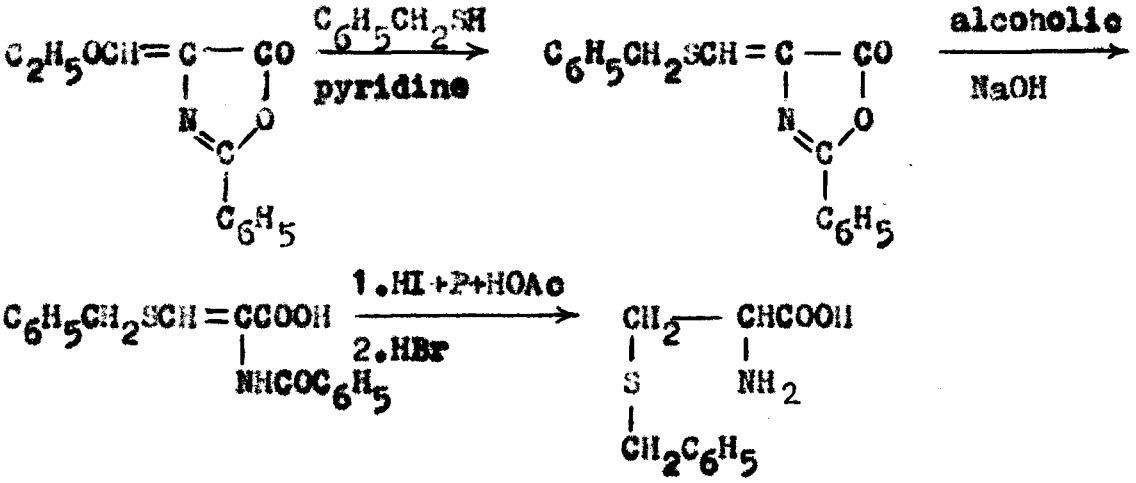
themselves by the use of small quantity of hydroiodic acid and red phosphorus in the presence of acetic acid. They obtained the amino acids themselves directly from the azlactones, or benzoylaminoacrylic acids or benzoylamino acids when large excess of hydroiodic acid was used. The following chart illustrates the preparations of benzoyl-phenylalanine and phenylalanine.



It is worth mentioning that in 1939 Herbst and Shemin (139) prepared phenylalanine in 65% over-all yield by the catalytic hydrogenation of α-acetaminocinnamic acid obtained from the corresponding azlactone, followed by hydrolysis.

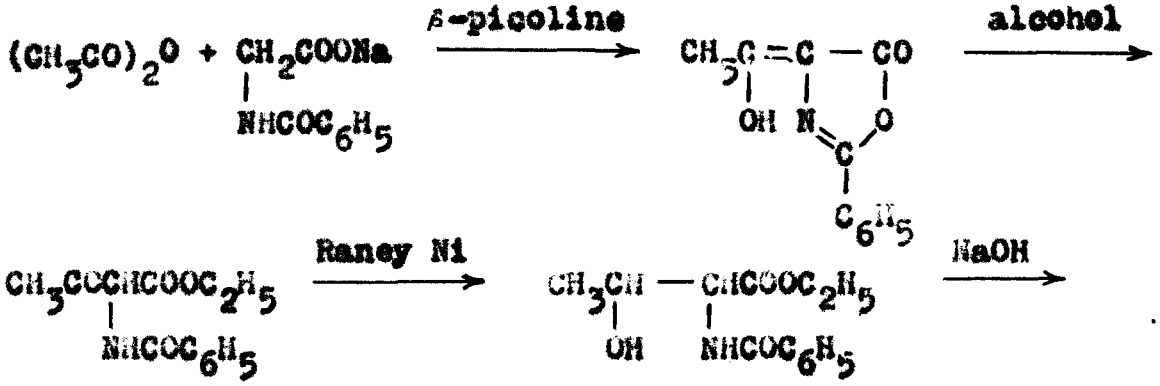
In 1952 valine-2-C^{14} was prepared by Adams and Tolbert (140) using azlactone method.

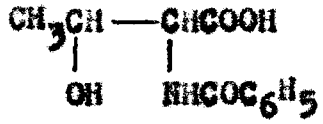
In 1955 Baltazzi and Davis (141) synthesised S-benzylcystein starting with 2-phenyl-4-ethoxymethylene-5-oxazolone, according to the following scheme:



Later Kaneko and Nakayama (142), Kaneko and coworkers (143) and Sasaki (144) did the syntheses of glutamic acid, tyrptophan and serine respectively starting with 2-phenyl-4-ethoxymethylene-5-oxazolone.

In 1948 Attenburrow and coworkers (145) prepared threonine by condensing acetic anhydride with sodium hippurate according to the following reactions:

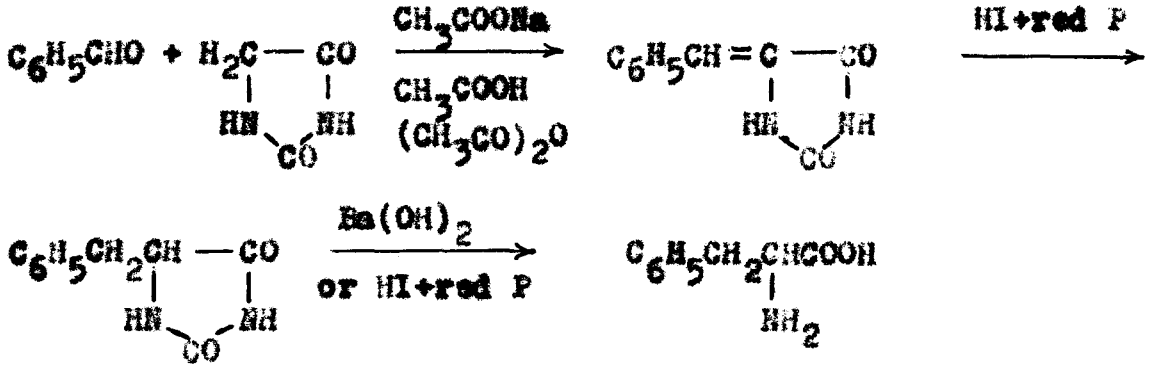




It has been seen that a number of naturally occuring α-amino acids were prepared by the azlactone method. Azlactone method may be considered as the best method for the syanthesee of phenylalanine and tyrosine. But the main advantage of this method over other methods is that it affords benzoyl derivatives of amino acids as intermediates, which are very useful in resolution, as already mentioned.

(b) Hydantoin method

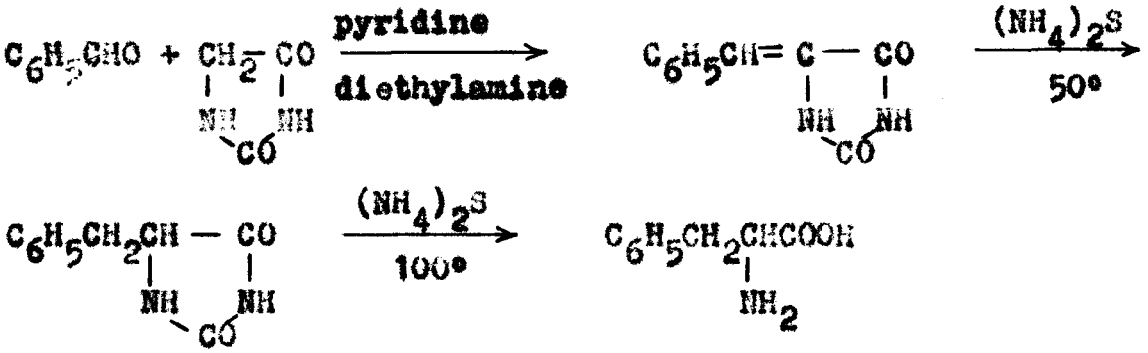
In 1911 Wheeler and Hoffmann (146) condensed benzaldehyde and anisaldehyde with hydantoin and converted the condensation products into phenyl alanine and tyrosine respectively in very good over-all yields. Thus starting from benzaldehyde and hydantoin phenylalanine was prepared as follows:



Tyrosine was similarly prepared. They also obtained 89.1% yield of tyrosine directly from anisalhydantoin on boiling

with hydroiodic acid in the presence of red phosphorus for several hours. Majima and Kotake (147) in their synthesis of tryptophan by this method used sodium amalgam for the reduction of the unsaturated hydantoin.

In 1935 Boyd and Robson (148,149) prepared phenylalanine in very high over-all yield using pyridine containing traces of diethylamine as condensing agent and ammonium sulphide as reducing and hydrolysing agents as follows:



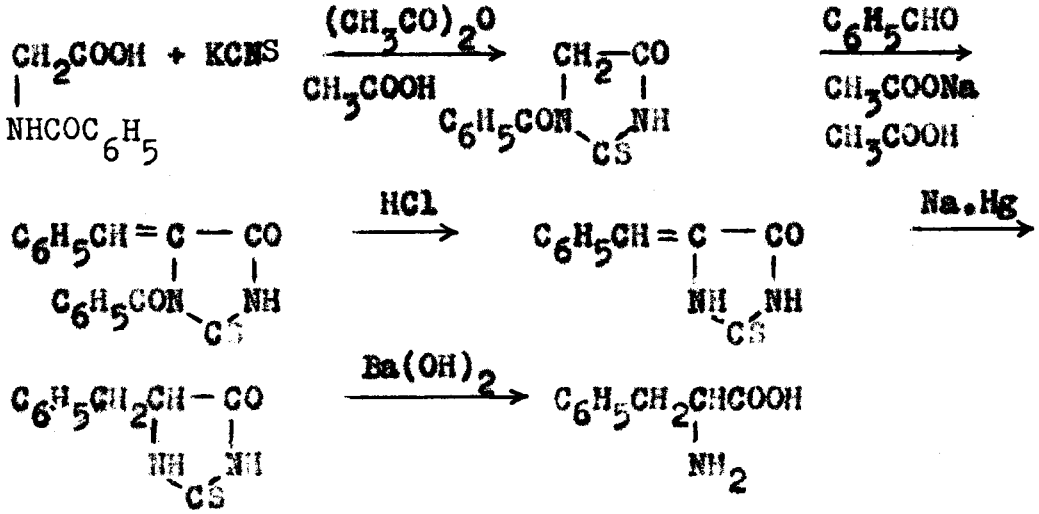
In the same year they (150) synthesised tryptophan also in good yield by an almost similar method.

Hydantoin method is superior to azlactone method in the synthesis of tryptophan.

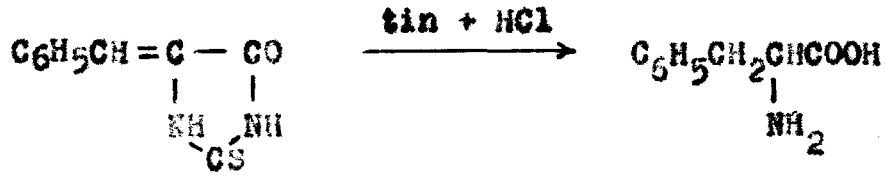
(c) <u>Thiohydantoin method</u>

In 1911 Johnson and Nicolet (151) obtained 86% yield of 2-thio-3-benzoylhydantoin when potassium thocyanate was heated with hippuric acid in the presence of acetic anhydride and glacial acetic acid. In the next year Johnson and O'Brien (152) prepared phenylalanine in very good over-all

yield starting with 2-thio-3-benzoylhydantoin and benzaldehyde according to the following scheme:



They also obtained phenylalanine in quantitative yield directly from 2-thio-4-benzal-hydantoin by the action of tin and hydrochloric acid on it.

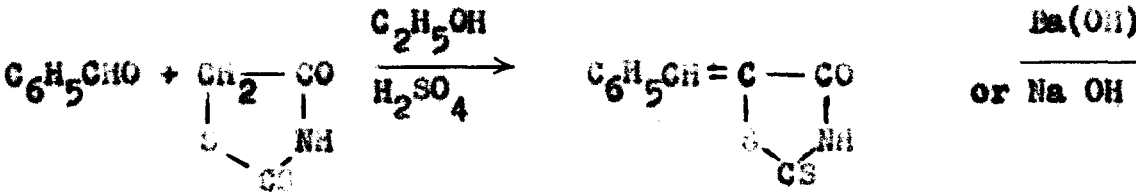


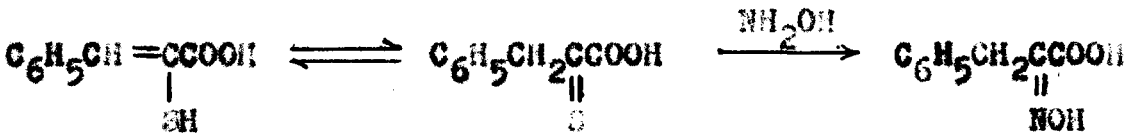
The thiohydantoin method for the synthesis of phenylalanine is easier and less expensive than hydantoin method.

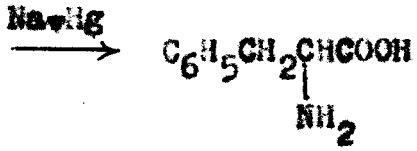
(d) Rhodanine method

In 1884 Nenoki (153) synthesised benzalrhodanine by condensing benzaldehyde with rhodanine. In 1903 anisal-rhodanine was similarly prepared by Andreasch and Zipser (154). Starting with them phenylalanine and O-methyltyrosine were synthesised only in 1922 and 1923 respectively and

these syntheses were carried out by Granacher (155,156) who observed for the first time that the hydrolysis product of benzalrhodanine is an equilibrium mixture of α-thiolcinnamic acid and phenylthiopyruvic acid and not α-thiolcinnamic acid alone as it had been observed by many investigators. Since there was thiopyruvic acid in equilibrium with α-thiolcinnamic acid the hydrolysis product could be completely converted into the oxime of phenylpyruvic acid. Then the oxime was reduced to phenylalanine.





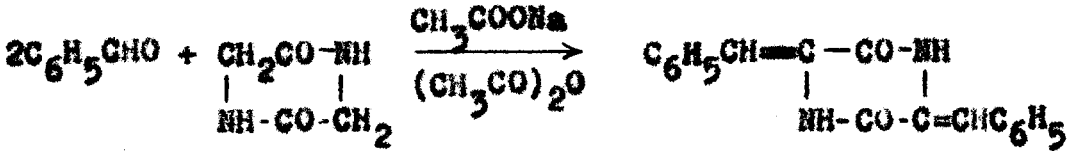


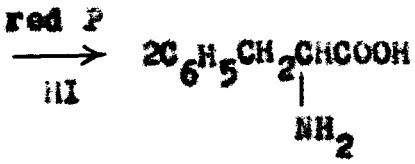
O-methyltyrosine was similarly prepared. In 1951 Gaudry and Mc Ivor (157) made some modification in Granacher method for the syntheses of phenylalanine and O-methyltyrosine.

(e) Diketopiperazine method

In 1921 Sasaki (158) developed a method for the syntheses of phenylalanine and tyrosine starting from glycine anhydride.

Thus phenylalanine was prepared in good over-all yield as follows:

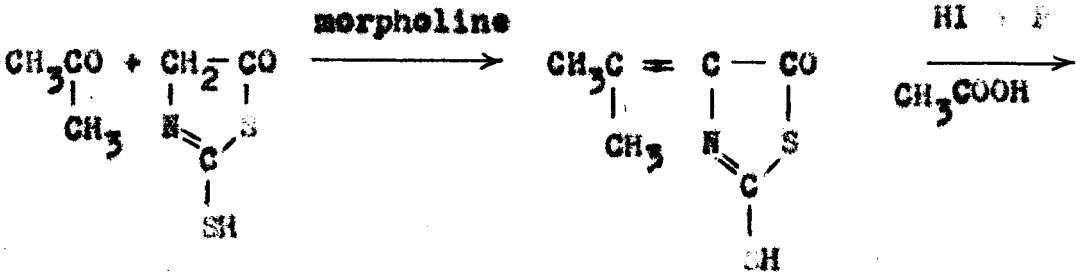


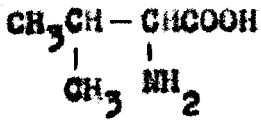


Tyrosine was similarly prepared.

(f) Mercaptothiazolone method

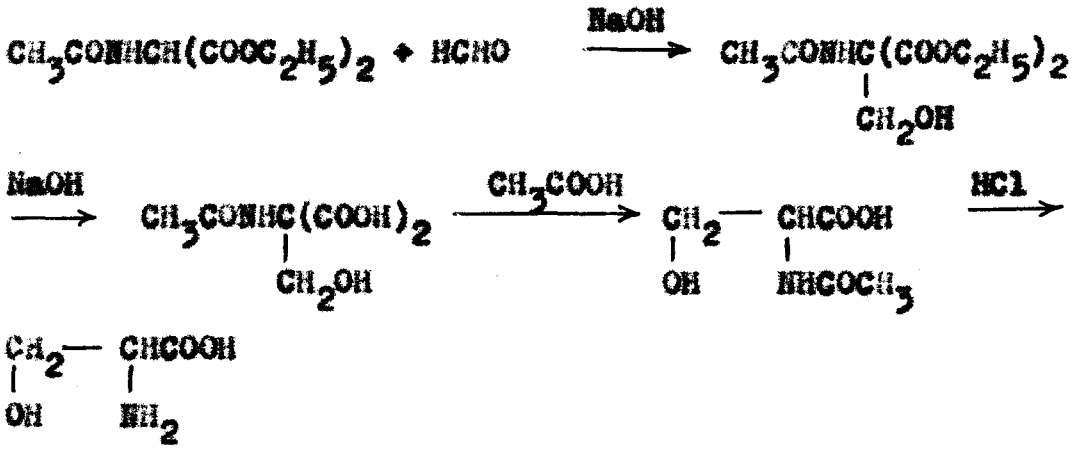
Billimoria and Cook (159) synthesised leucine, valine, phenylalanine, tyrosine, methionine and norleucine in good yields from the condensation products of appropriate aldehydes and ketones with 2-mercapto-5(4H)-thiazolone. Thus valine was prepared according to the following scheme:





(g) Other methods

In 1947 King (160,161) accomplished the synthesis of serine by condensing formaldehyde with acetamidomalonic ester as follows:



Kawasaki (162) in 1957 condensed formaldehyde with acetamide-acetoacetic ester and directly hydrolysed the condensation product to serine. In 1956 Mahajani and Ray (163,164) prepared serine, threonine and tyrosine by condensing appropriate aldehydes with methyleneaminoacetonitrile. Serine was synthesised in 1959 by Akabori and coworkers (165) starting with formaldehyde and glycine.

...

IV: α-KETO ACID METHODS

(a) Reduction of keto acids in the presence of ammonia

In 1899 Erlenmeyer and Kunlin (166) obtained N-phenylacetylphenylalanine when phenylpyruvic acid was reduced in the presence of ammonia. Phenacetylphenylalanine afforded phenylalanine on hydrolysis:

$$2C_6H_5CH_2COCOOH \xrightarrow{NH_3,H_2} C_6H_5CH_2\underset{\displaystyle NHCOCH_2C_6H_5}{\underset{|}{C}}HCOOH \xrightarrow{\text{hydrolysis}}$$

$$C_6H_5CH_2\underset{\displaystyle NH_2}{\underset{|}{C}}HCOOH$$

De Jong (167) obtained acetylalanine by the reduction of ammonium pyruvate.

Knoop and Oesterlin (168,169) prepared α-aminobutyric acid, aspartic acid, glutamic acid and phenylalanine according to the following scheme:

$$RCOCOOH + NH_3 \xrightarrow{Pd,H_2} R\underset{\displaystyle NH_2}{\underset{|}{C}}HCOOH$$

The yields were good in the case of phenylalanine and α-aminobutyric acid. In 1939 Schoenheimer and Ratner (69) prepared in good yields alanine, norleucine, phenylalanine, tyrosine, glutamic acid and aspartic acid containing isotopic nitrogen by the hydrogenation of the corresponding keto acids in the presence of ammonia containing isotopic nitrogen,

using the method of Knoop and Oesterlin. The products were pure. Palladium, platinum or Raney nickle were used as catalyst by other investigators (170,174) for the preparation of glycine, alanine and other amino acids.

The main drawback of this method is the non-availability of the desired α-keto acids.

(b) Reduction of Oximes of α-keto acids

(i) Oximes from keto acids:

In 1880 Gutknecht (175) synthesised alanine by the reduction of pyruvic acid oxime.

$$CH_3COCOOH \xrightarrow[HNO_3]{NH_2OH} CH_3C(=NOH)COOH \xrightarrow[HCl]{Zn} CH_3CH(NH_2)COOH$$

A few years later Piutti (176) carried out his classical synthesis of aspartic acid according to the following scheme:

$$CH(COOC_2H_5)_2 + CH_3COOC_2H_5 \xrightarrow{Na} COC(COOC_2H_5)_2CH_2COOC_2H_5 \xrightarrow{Na}$$

$$CNaC(COOC_2H_5)_2COCH_2COOC_2H_5 \xrightarrow[NH_2OH.HCl]{heat} C(=NOH)CH_2CH(COOC_2H_5)_2 \xrightarrow{Na.Hg} CH(NH_2)CH_2COONa \cdot COONa$$

Baugess and Berg (177) and Shemin and Herbst (178) reduced keto acid oximes using nickel and platinum oxide catalysts respectively. Shemin and Herbst obtained 85 % yield of alanine and 80% yield of phenylalanine from the oximes of the corresponding keto acids.

(ii) Oximes from substituted malonic esters

In 1902 Fischer and Weigert (179) synthesised lysine as follows:

$$CNCH_2CH_2CH_2Cl + NaCH(COOC_2H_5)_2 \xrightarrow{NaOC_2H_5}$$

$$CNCH_2CH_2CH_2CH(COOC_2H_5)_2 \xrightarrow{C_2H_5NO_2} CNCH_2CH_2CH_2C(=NOH)COOC_2H_5$$

$$\xrightarrow[C_2H_5OH]{Na} CH_2(CH_2)_3CH(NH_2)COOH$$

In 1951 Floyd and Miller (180) prepared lysine by the reduction of the oxime formed when 4-benzoylaminobutylmalonic ester was treated with butyl nitrite and sodium ethoxide.

Onishchenko (181) prepared phenylalanine and leucine in good yields according to the following scheme:

$$RCH(COOH)_2 \xrightarrow{NOCl} RC(=NOH)COOH \xrightarrow{Sn + HCl} RCH(NH_2)COOH$$

In 1947 Shivers and Hauser (182) synthesised the esters of norleucine, phenylalanine and N,N-diethyl ornithine by the

hydrogenation of the oximes obtained from substituted malonic ester on treating with ethyl nitrite and sodium ethoxide.

In 1956 Inui and Kaneko (183) accomplished the synthesis of isoleucine as follows:

$$NaCH(COOC_2H_5)_2 \xrightarrow[\text{sulphonate}]{\text{sec.butyl p-toluene}} CH_3CH_2\underset{\underset{CH_3}{|}}{C}HCH(COOC_2H_5)_2$$

$$\xrightarrow[NaOC_2H_5]{C_4H_9NO_2} CH_3CH_2\underset{\underset{CH_3}{|}}{C}H-\overset{\overset{NOH}{||}}{C}COOH \xrightarrow{Na.Hg.} CH_3CH_2\underset{\underset{H_3C}{|}}{C}H-\underset{\underset{NH_2}{|}}{C}HCOOH$$

(iii) <u>Oximes from substituted acetoacetic esters</u>

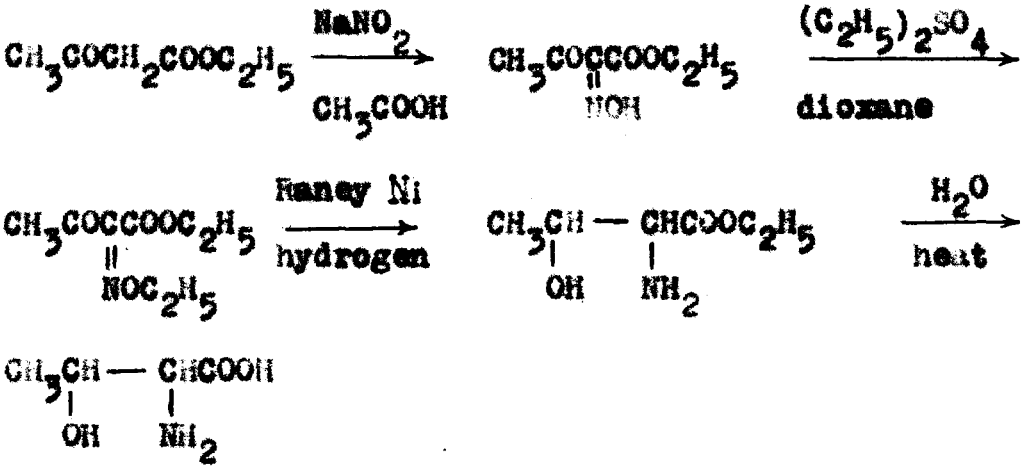
Bouveault and Locquin (184-186) prepared leucine and isoleucine by the reduction of the oximino esters obtained from substituted acetoacetic esters. Thus isoleucine was prepared as follows:

$$CH_3CH_2\underset{\underset{CH_3}{|}}{C}H-\underset{\underset{COCH_3}{|}}{C}HCOOC_2H_5 \xrightarrow[\text{sulphate}]{\text{nitrosyl}} CH_3CH_2\underset{\underset{CH_3}{|}}{C}H-\overset{\overset{NOH}{||}}{C}COOC_2H_5$$

$$\xrightarrow[C_2H_5OH]{Zn + HCl} CH_3CH_2\underset{\underset{CH_3}{|}}{C}H-\underset{\underset{NH_2}{|}}{C}HCOOC_2H_5 \xrightarrow[NaOH]{\text{dilute}} CH_3CH_2\underset{\underset{CH_3}{|}}{C}H-\underset{\underset{NH_2}{|}}{C}HCOOH$$

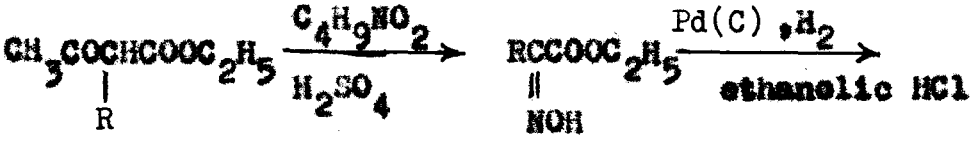
Schmidt and Widmann (187) accomplished the synthesis of aspartic acid by Bouveault-Locquin method. Threonine was

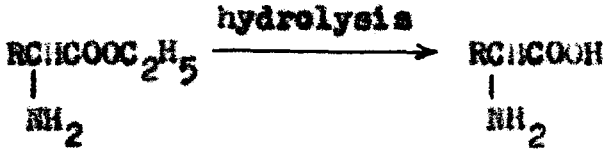
synthesised by Adkin and Reeve (188) from unsubstituted acetoacetic ester.



Lure and coworkers (189) prepared a mixture of allothreonine and threonine in 72% yield from the above unsubstituted oxime. McIlwain and Richardson (190) prepared glutamic acid in good yield and hydroxyproline in poor yield using Bouveault-Locquin method.

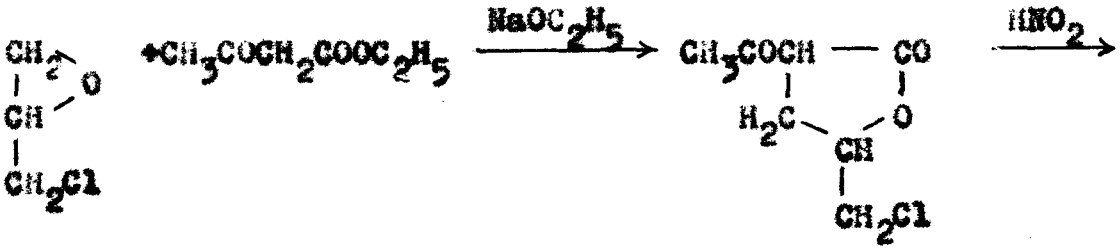
In 1942 Hamlin and Hartung (191) improved much the Bouveault-Locquin method for the syntheses of α-amino acids by the introduction of butyl nitrite-sulphuric acid mixture as nitrosating agent and palladium on charcoal catalyst in the presence of ethanolic hydrogen chloride for the hydrogenation of the oximes. Thus they prepared phenylalanine, tyrosine, isoleucine and a number of other amino acids in excellent yields.

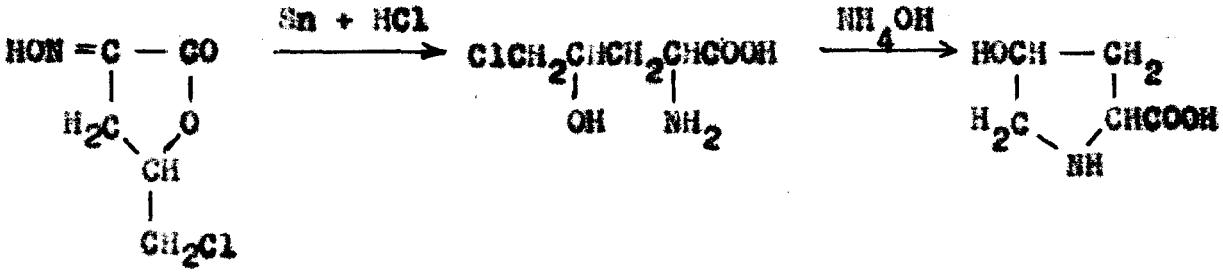




(iv) Oximes from acetylbutyrolactones

Feofilaktov (192,193) synthesised hydroxyproline from the acetobutyrolactone obtained by the action of epichlorohydrin on acetoacetic ester.





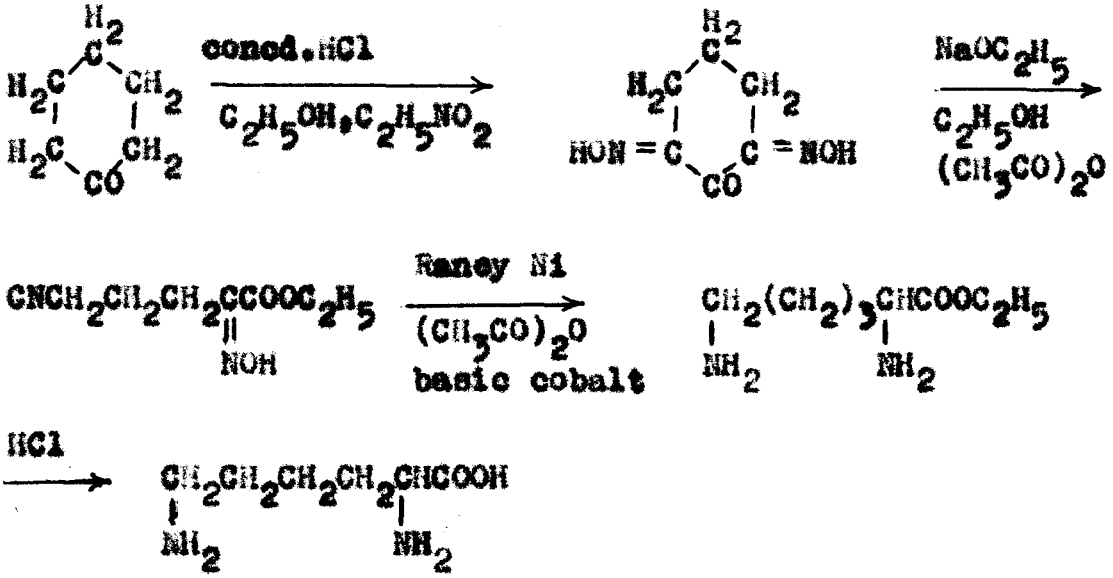
Mcllwain and Richardson (190) also did the synthesis of hydroxyproline essentially by this method.

Snyder et al. (194-196) prepared methionine starting with α-aceto-γ-butyrolactone.

(v) Oximes from cyclo ketones:

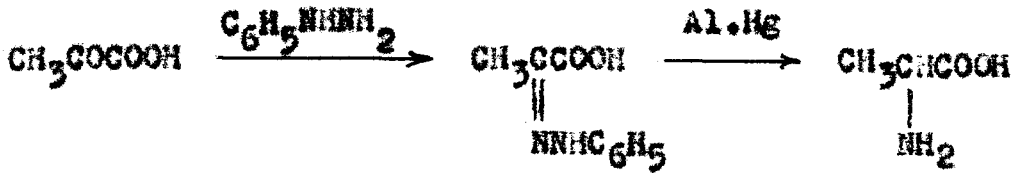
In 1960 Ferris and coworkers (197-200) synthesised

lysine in 63 % over-all yield starting with cyclohexanone as follows:



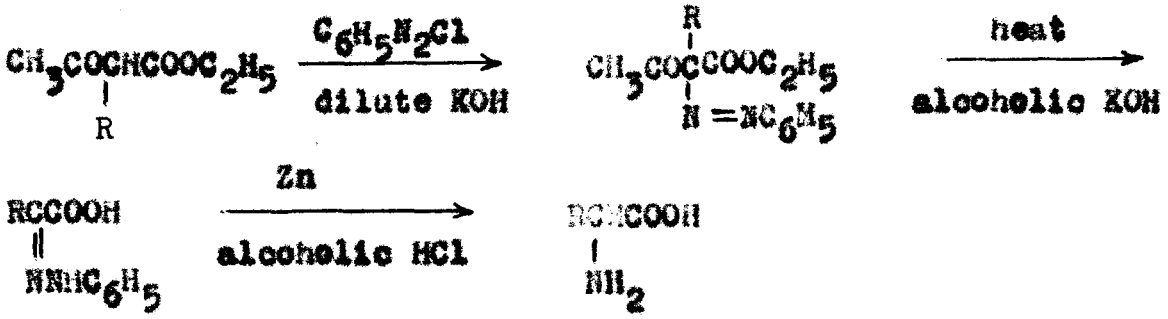
(c) Reduction of phenylhydrazones of α-keto acids

Fischer and Groh (201) obtained a small yield of alanine on reducing phenylhydrazone of pyruvic acid with aluminium amalgam.



Feofilaktov and collaborators (202,210) prepared alanine, leucine, isoleucine, norleucine, valine, phenylalanine, tyrosine and glutamic acid in excellent yields by the reduction of the phenylhydrazones of α-keto acids obtained by coupling benzenediazonium chloride with substituted acetoacetic esters. Zinc and alcoholic hydrogen chloride

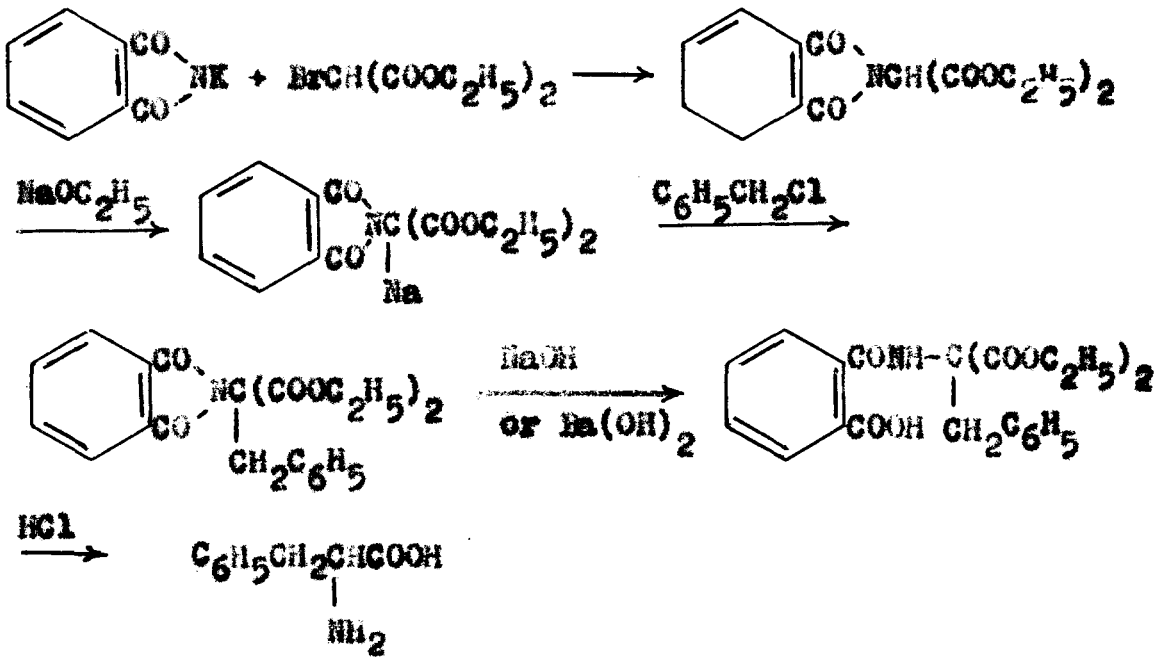
was used for the reduction of the phenylhydrazones.



V. AMINOMALONIC ESTER AND RELATED METHODS

(a) Phthalimidomalonic ester method

In 1903 Sorensen (211) developed a method for the syntheses of α-amino acids using phthalimidomalonic ester as starting material. Thus Sorensen (211,212) synthesised phenylalanine according to the following scheme:



Sorensen (211,212) used this method also for the syntheses of lysine and ornithine. Proline was prepared by Sorensen and Anderson (213,214) making use of this method.

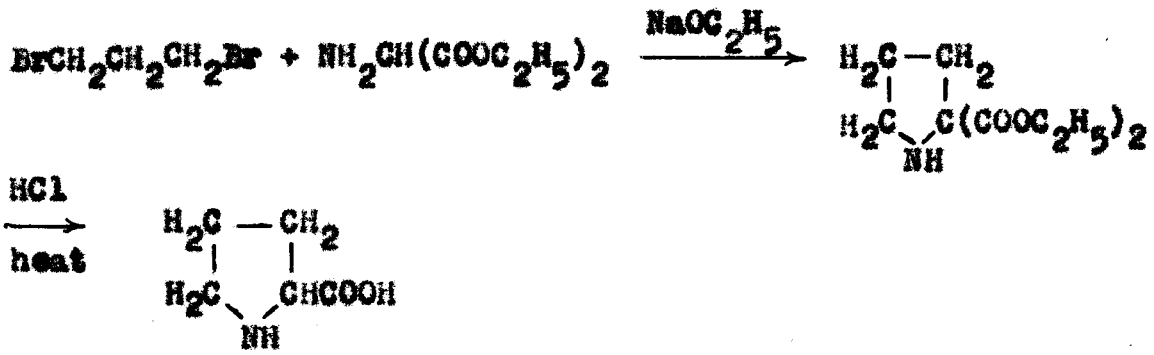
In 1914 Stephen and Wiezmann (215) employed phthalimidomalonic ester method for the syntheses of tyrosine and 3,4-dihydroxyphenylalanine. In 1916 Hammarsten (216) did the synthesis of hydroxyproline starting with allylglycine

which was prepared from phthalimidomalonic ester by Sorensen (217). Aspartic acid was prepared by Dunn and Smart (218,219) in 1930, Serine by Mitra (220) in 1930, and methionine by Barger and Weichselbaum (221,222) in 1931 using this method. In 1939 Wood and du Vigneaud (223) did the synthesis of cystine by this method.

The difficulty encountered in the removal of the phthaloyl residue is the main drawback of this method.

(b) <u>Aminomalonic ester method</u>

In 1923 Putochin (224) synthesised proline starting with aminomalonic ester as follows:



Locquin and Cerchez (225-227) in 1930 prepared glycine, leucine and phenylalanine by condensing sodioaminomalonic ester with appropriate alkyl halides and hydrolysing the condensation products with superheated steam. The difficulty in the preparation of aminomalonic ester and the possibility of N-alkylation are the drawbacks of this method.

(c) Benzamidomalonic ester method

Dunn, Redemann and their coworkers (228-230) used benzamidomalonic ester in the preparation of alanine, aspartic acid, glutamic acid, leucine, valine, phenylalanine and glycine. The yields were very good. Thus phenylalanine was prepared as follows:

$$HON{=}C(COOC_2H_5)_2 \xrightarrow{Al,H_2} NH_2CH(COOC_2H_5)_2 \xrightarrow[Na_2CO_3]{C_6H_5COCl}$$

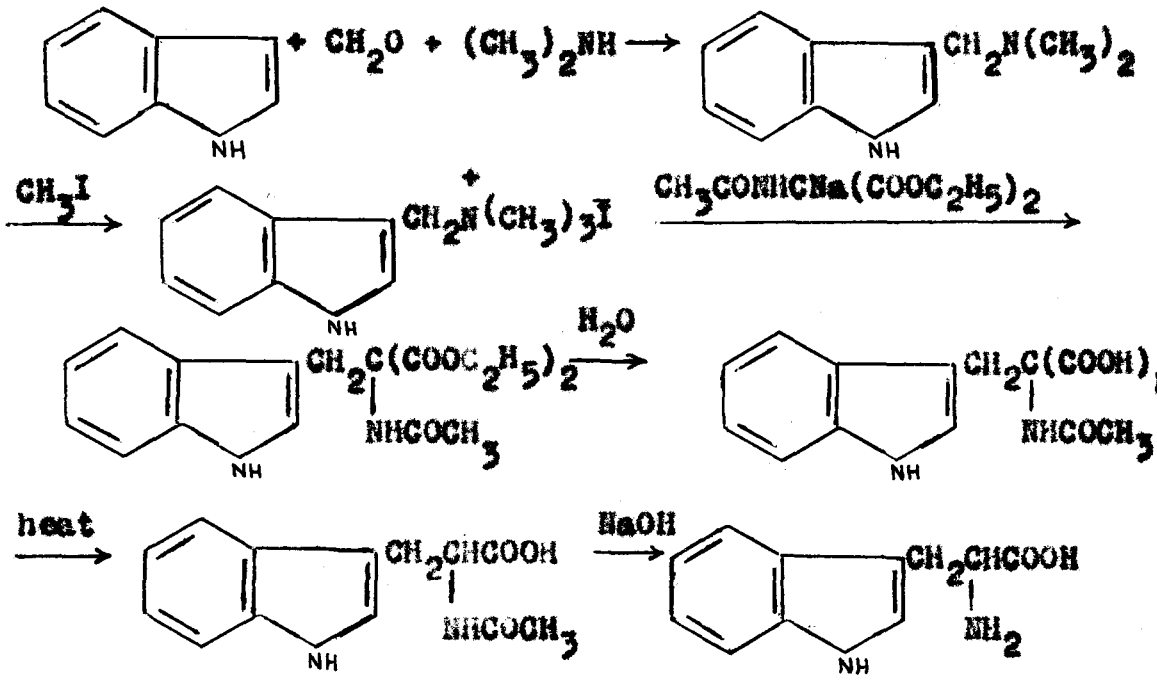
$$C_6H_5CONHCH(COOC_2H_5)_2 \xrightarrow[C_6H_5CH_2Cl]{NaOC_2H_5} C_6H_5CH_2\underset{\displaystyle NHCOC_6H_5}{\overset{\displaystyle |}{C}}(COOC_2H_5)_2 \xrightarrow{HBr}$$

$$C_6H_5CH_2\underset{\displaystyle NH_2}{\overset{\displaystyle |}{C}}HCOOH$$

The main advantage of benzamidomalonic ester method over phthalimidomalonic ester method is that the substituted benzamidomalonic esters can be readily hydrolysed and decarboxylated to give the amino acids.

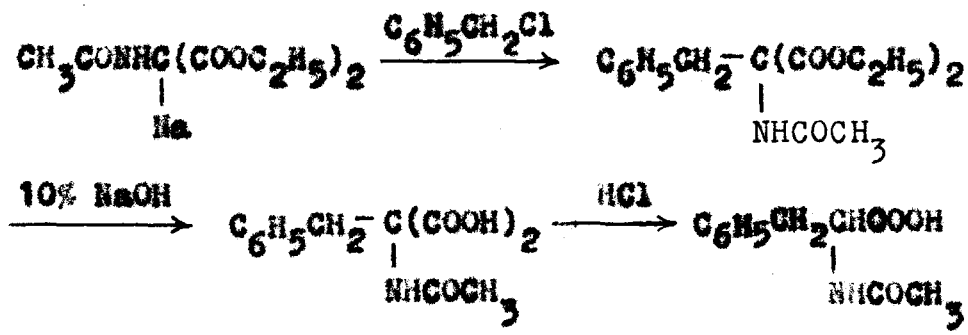
(d) Acetamidomalonic ester method

In 1944 Snyder and Smith (231,232) and Albertson et al. (233) introduced acetamidomalonic ester for the syntheses of α-amino acids. Snyder and coworkers (231,232) synthesised tryptophan in 45% over-all yield starting from indole according to the following reactions:



Albertson et al.(233) prepared tryptophan by a similar method.

In the next year Snyder et al. (234-236) synthesised the acetyl derivatives of phenylalanine, leucine, norleucine and norvaline starting from acetamidomalonic ester and hydrolysed them to the amino acids. Thus acetylphenylalanine was prepared in excellent yield as follows:



In 1945 Albertson and Archer (237-239) synthesised histidine, leucine, and phenylalanine in excellent yields starting with

acetamidomalonic ester. They carried out the saponification, decarboxylation and deacetylation of the substituted acetamidomalonates in a single step with constant boiling hydrochloric acid or hydrobromic acid.

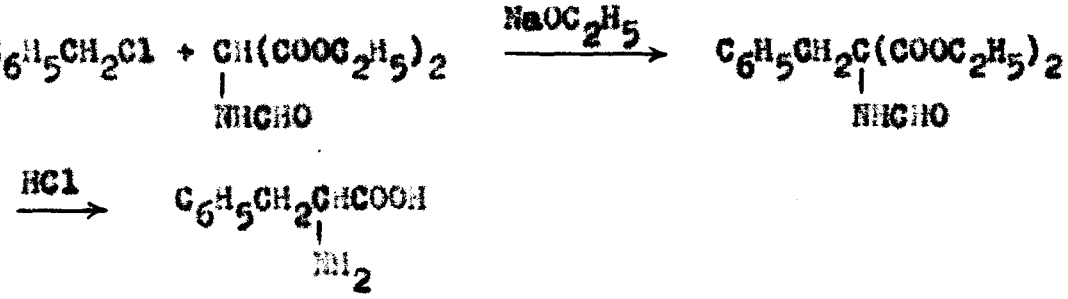
In 1953 Atkinson and coworkers (240) and in 1959 Joullie et al. (241) synthesised cystine in very good yield using acetamidomalonic ester. Kato et al. (242-244) employed this method in the syntheses of ornithine and glutamic acid. In 1954 Servigne and Saarvasi (245) did the synthesis of lysine while Hellmann and Lingens (246) did that of phenylalanine and tryptophan. Vanderweele and White (247) prepared tryptophan, phenylalanine and glycine and their acetylderivatives using acetamidomalonic ester. In 1959 Yuan and coworkers (248) accomplished the synthesis of proline.

The main advantage of this method over benzamidomalonic ester method is that the removal of the acetyl group is much easier than that of benzoyl group.

(e) Formamidomalonic ester method

In 1947 Galat (249) employed formylaminomalonic ester which can be prepared in a substantially higher yield than acetamidomalonic ester in the syntheses of α-amino acids. He did the syntheses of phenylalanine, aspartic acid and

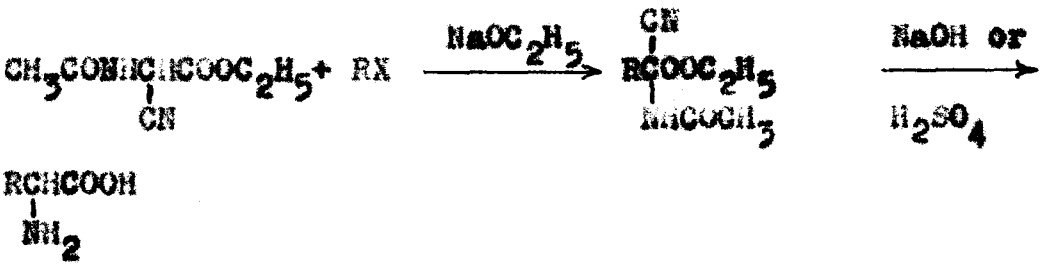
glutamic acid in good yields. Thus phenylalanine was synthesised as follows:



In 1949 Cohen et al. (250) prepared phenylalanine and norleucine in very good yield by this method. Capkova-Jirku and coworkers (251) prepared proline and hydroxyproline using formamidomalonic ester. In 1954 Hellmann and Lingens (246) did the synthesis of tryptophan. Meek and coworkers (252) in 1959 employed this method for the syntheses of phenylalanine, tyrosine, norleucine and aspartic acid.

(f) <u>Acetamidocyanoacetic ester method</u>

In 1945 Albertson and Tullar (253) synthesised tryptophan, methionine, valine, leucine and phenylalanine in excellent yields by condensing appropriate alkyl halides with acetamidocyanoacetic ester and hydrolysing the condensation product in acidic or basic media.



The over-all yields of these amino acids were lower in the case of acetamidomalonic ester method. Moreover valine could not be prepared using acetamidomalonic ester because isopropyl bromide did not condense with it.

Albertson and Archer (238,254) prepared histidine, phenylalanine and valine using acetamidocyanoacetic ester method. In 1948 Ohta (255) used this method for the syntheses of phenylalanine, norleucine, norvaline and α-aminobutyric acid.

(g) Phenylacetamidocyanoacetic ester method

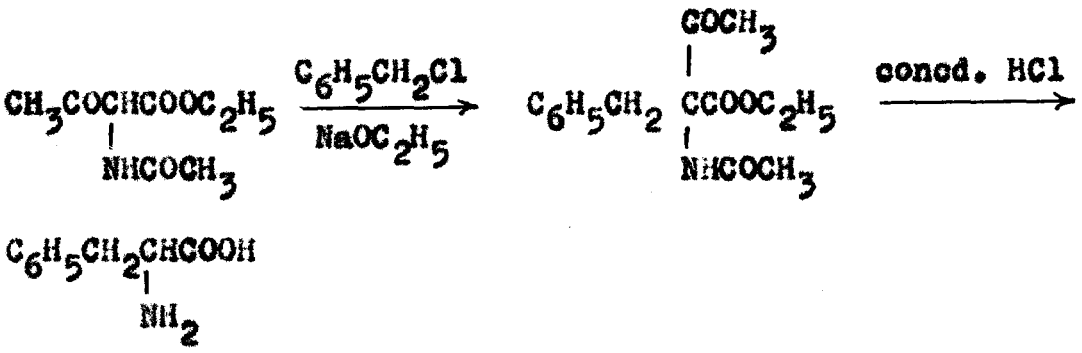
In 1949 Ehrhart (256) employed phenylacetamidocyanoacetic ester in the syntheses of phenylalanine, p-methoxyphenylalanine, leucine and valine. Thus phenylalanine was prepared according to the following reactions:

$$C_6H_5CH_2CONHCH(CN)COOC_2H_5 + C_6H_5CH_2Cl \xrightarrow{NaOC_2H_5} C_6H_5CH_2C(CN)(NHCOCH_2C_6H_5)COOC_2H_5$$

$$\xrightarrow{HBr} C_6H_5CH_2CH(NH_2)COOH$$

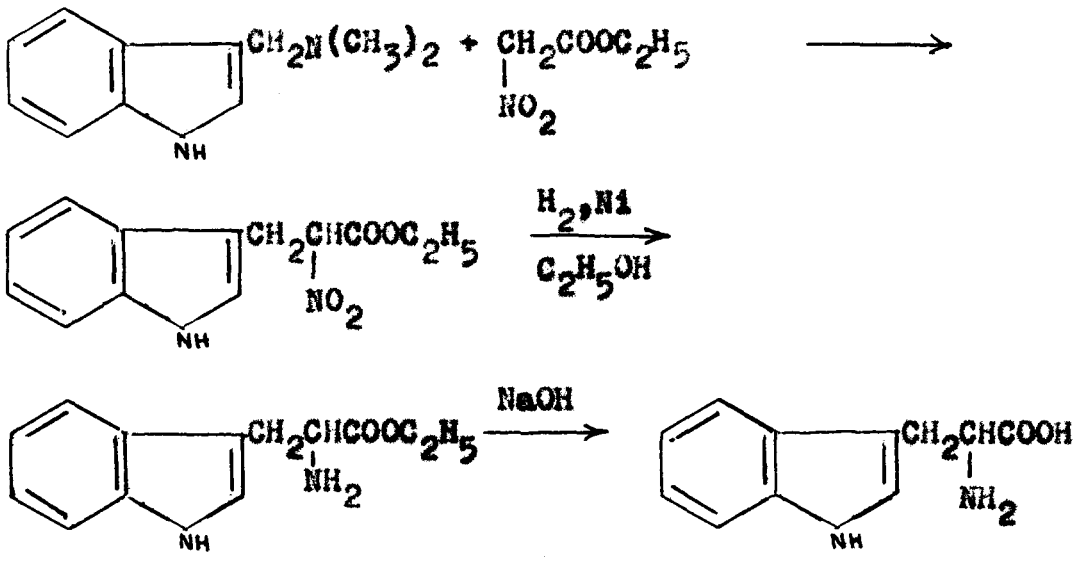
(h) Acetamidoacetoacetic ester method

In 1957 Kawasaki (162) introduced acetamidoacetoacetic ester for the syntheses of α-amino acids. He synthesised phenylalanine according to the following scheme:



(i) Nitroacetic and Nitromalonic ester methods

Weisblat and Lyttle (257,258) used nitroacetic ester in the syntheses of tryptophan, threonine and leucine. Thus tryptophan was synthesised as follows:



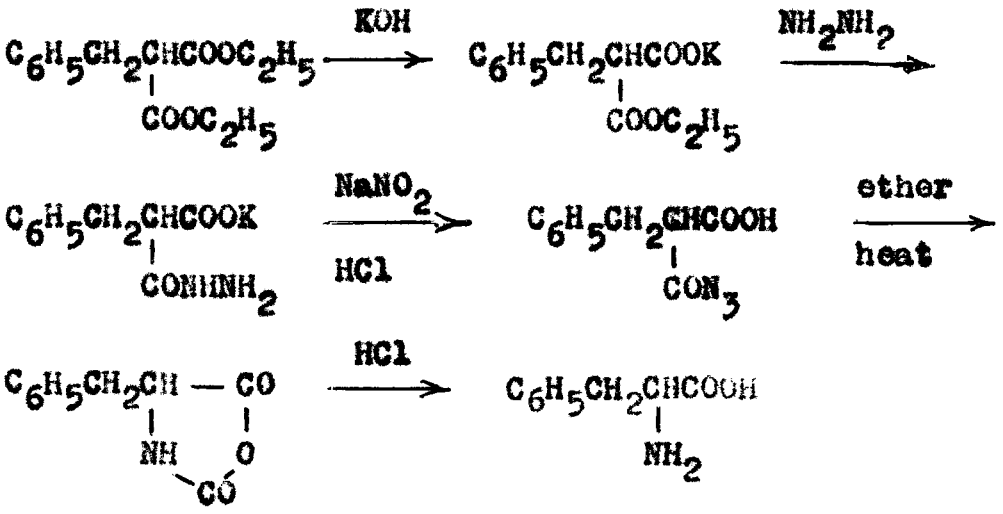
In 1949 Weisblat and Lyttle (259) employed nitromalonic ester instead of nitroacetic ester for the synthesis of tryptophan. The yields were excellent in every step.

VI. AZIDE SYNTHESIS

(a) Curtius method

(1) From malonic ester

In 1921 Curtius and Sieber (260) developed a method for the syntheses of α-amino acids starting from substituted malonic esters. Alkyl substituted malonic esters were converted into alkyl malonazidic acids and from them the amino acids were prepared through the isatoic anhydrides polymeric anhydrides or urethans. Curtius and Sieber (260-262) prepared glycine, alanine, phenylalanine, α-aminobutyric acid, leucine and valine by this method. Thus phenylalanine was prepared through isatoic anhydride according to the following scheme:



(ii) From cyanoacetic ester

In 1936 Sah (263) introduced the azides of cyanoacetic

ester for the syntheses of α-amino acids. He prepared glycine as follows:

$$CNCH_2COOC_2H_5 \xrightarrow{NH_2NH_2H_2O} CNCH_2CONHNH_2 \xrightarrow[HCl]{NaNO_2} CNCH_2CON_3$$

$$\xrightarrow[ether]{C_2H_5OH} CNCH_2NHCOOC_2H_5 \xrightarrow[2.H_2SO_4]{1.Ba(OH)_2} \begin{matrix} CH_2COOH \\ | \\ NH_2 \end{matrix}$$

Darapsky et al. (264) synthesised norvaline, and leucine from substituted cyanoacetic esters by this method. They hydrolysed the urethanes with hydrochloric acid. Gagnon et al. (265,266) prepared phenylalanine, valine and a number of other amino acids in good over-all yields.

(b) Schmidt method

(i) From Acetoacetic ester

In 1924 Schmidt (267) prepared glycine, phenylalanine, leucine, aspartic acid and α-aminobutyric acid in excellent yields by the action of hydrazoic acid on substituted acetoacetic esters followed by the hydrolysis of the resulting acetyl amino esters. Thus phenylalanine was prepared according to the following reactions:

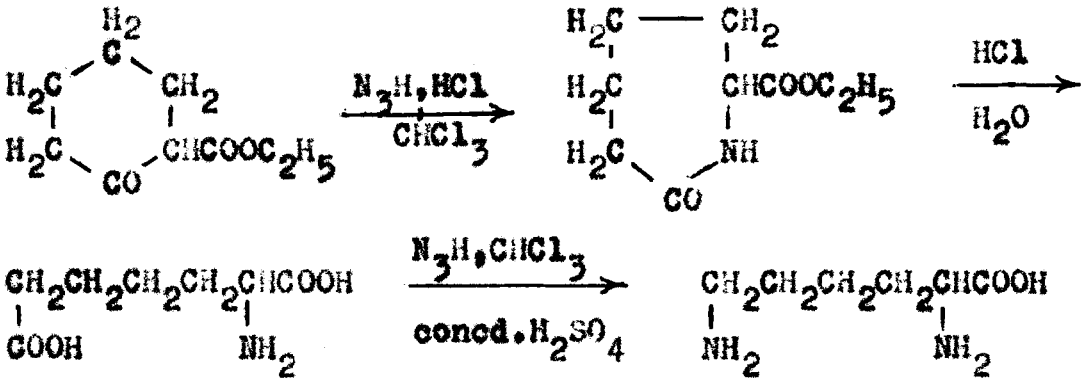
$$\begin{matrix} CH_3COCHCOOC_2H_5 \\ | \\ CH_2C_6H_5 \end{matrix} + N_3H \xrightarrow[C_6H_5]{conc.\ H_2SO_4} \begin{matrix} CH_3CONHCHCOOC_2H_5 \\ | \\ CH_2C_6H_5 \end{matrix}$$

$$\xrightarrow{hydrolysis} \begin{matrix} C_6H_5CH_2CHCOOH \\ | \\ NH_2 \end{matrix}$$

Hayashi (268) in 1958 subjected dialkyl substituted acetoacetic esters to Schmidt reaction and obtained a mixture of two or three amino acids in each case. Thus he obtained alanine and α-methyl alanine from ethyl dimethylacetoacetate. Ethylmethylacetoacetic ester afforded a mixture of alanine, α-methyl alanine and α-aminobutyric acid.

(ii) <u>From cycloketone-2-carboxylic esters and nitriles</u>

Adamson (269) synthesised lysine and ornithine from cyclohexanone-2-carboxylic ester and cyclopentanone-2-carboxylic ester by a two fold Schmidt reaction. Thus lysine was prepared in 54% over-all yield according to the following scheme:



In the case of ornithine also the over-all yield was very good.

In 1951 Shechter and Kirk (270) synthesised lysine in 59.5% yield from 2-cyanocyclohexanone by Schmidt method.

(iii) From malonic acid

In 1939 Adamson (269) obtained 46% yield of glycine on treating malonic acid with hydrazoic acid in presence of sulphuric acid.

$$CH_2(COOH)_2 + N_3H \xrightarrow{\text{concd. } H_2SO_4} \underset{\displaystyle NH_2}{\overset{\displaystyle CH_2COOH}{|}}$$

Briggs et al. (271) synthesised phenylalanine in 16% yield from benzylmalonic acid. Takagi and Hayashi (272) successfully employed Schmidt reaction in the syntheses of a number of amino acids from substituted malonic acids.

(c) Hofmann degradation method

In 1942 Li et al. (273) used Hofmann degradation for the synthesis of the α-amino acid isovaline as follows:

$$CH_3CH_2\underset{\displaystyle CN}{\overset{\displaystyle CH}{|}}COOC_2H_5 \xrightarrow[CH_3I]{NaOC_2H_5} CH_3CH_2\underset{\displaystyle CH_3}{\overset{\displaystyle C(CN)}{|}}COOC_2H_5 \xrightarrow[H_2SO_4]{\text{concd.}}$$

$$CH_3CH_2\underset{\displaystyle CH_3}{\overset{\displaystyle COOH}{|}}CCONH_2 \xrightarrow[\text{dilute NaOH}]{Br_2} CH_3CH_2\underset{\displaystyle CH_3}{\overset{\displaystyle CONHBr}{|}}CCOOH \xrightarrow[70^\circ]{\text{concd.KOH}}$$

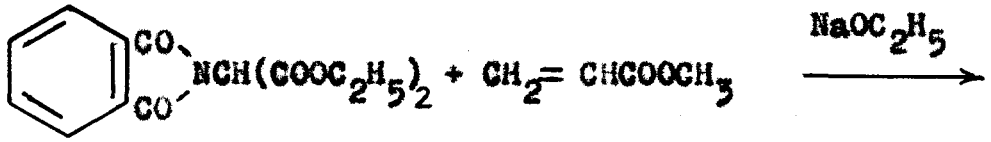
$$CH_3CH_2\underset{\displaystyle CH_3}{\overset{\displaystyle C(NH_2)}{|}}COOH$$

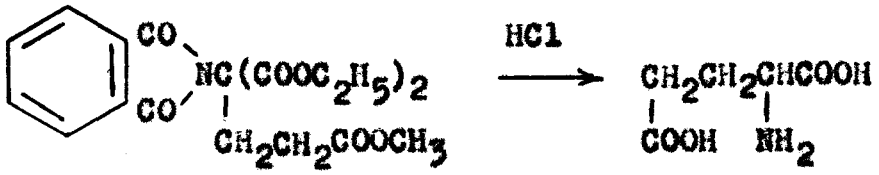
In 1947 they (274,275) prepared valine, leucine and norleucine by this method.

VII. MICHAEL CONDENSATION METHOD

(a) From acrylic ester

In 1938 Marvel and Stoddard (276) synthesised glutamic acid in about 75% yield by the Michael condensation of methyl acrylate with phthalimidomalonic ester followed by the hydrolysis of the condensation product.





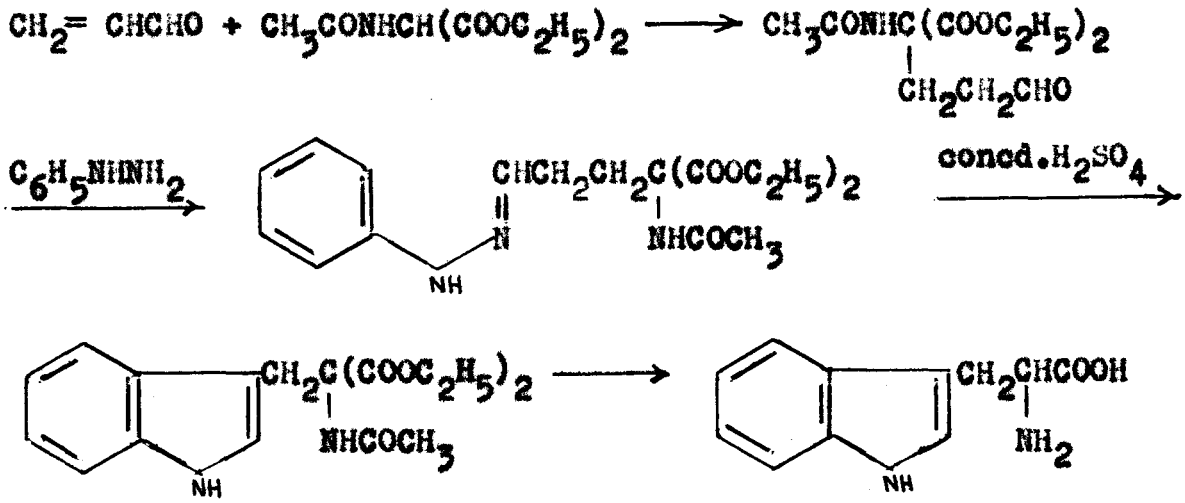
In 1945 Snyder et al. (234) prepared glutamic acid starting with methyl acrylate and acetamidomalonic ester in a similar line. In 1952 Weisblat and Lyttle (277) did the synthesis of glutamic acid from the Michael condensation product of ethyl acrylate and ethyl nitroacetate.

Wieland et al. (278) prepared glutamic acid by the hydrolysis of the condensation product of malonic ester with methyl-α-phenylacetylaminoacrylate. Hellmann and Lingens (279) obtained a Michael condensation product on heating a mixture of malonic ester, formaldehyde and an acetylaminomalonic ester and the condensation product

afforded glutamic acid on hydrolysis.

(b) <u>From acrolein</u>

In 1948 Warner and Moe (280,281) synthesised glutamic acid starting with acrolein and acetamidocyanoacetic ester. Warner and Moe (280) did the synthesis of tryptophan according to the following scheme:

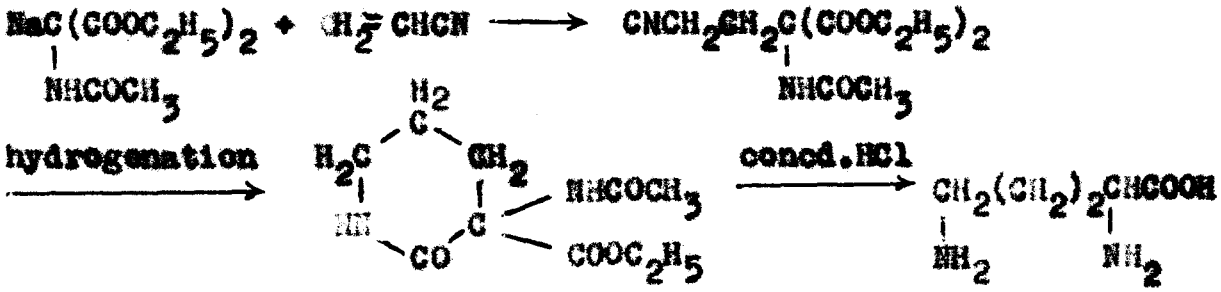


They (280) prepared ornithine from the above phenylhydrazone of ethyl-γ,γ-dicarbethoxy-γ-acetamidobutyraldehyde. In 1955 Grudzinski and Kotelko (122) and in 1957 Chibata and Yamada (282) improved Warner-Moe synthesis of tryptophan from acrolein and acetamidomalonic ester.

In 1950 Warner and Moe (283) synthesised lysine starting with acrolein and acetamidomalonic ester. Okuda (284) prepared proline from the condensation product of acrolein with nitromalonic ester.

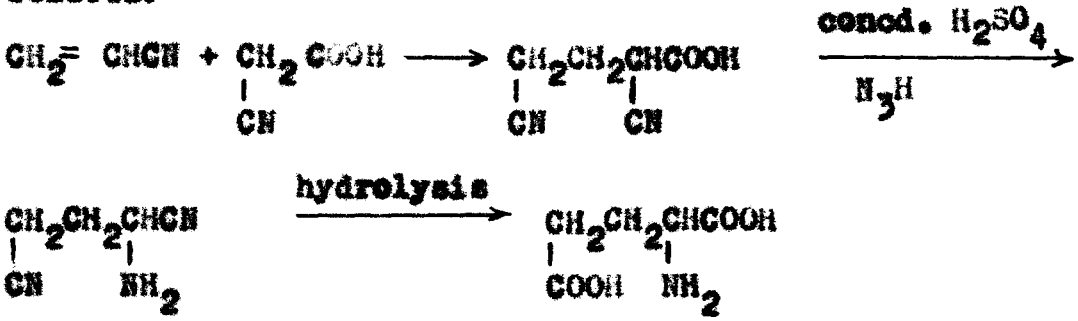
(c) From acrylonitrile

Albertson and Archer (285) in 1950 accomplished the synthesis of ornithine according to the following scheme:



Kovacs and Vincze (286) synthesised ornithine starting with acrolein and dimethyl acetamidomalonate in a similar line. Akabori et al. (287) used nitromalonic ester in the place of acetamidomalonic ester in the synthesis of ornithine.

In 1958 Schmuth (288) prepared glutamic acid as follows:

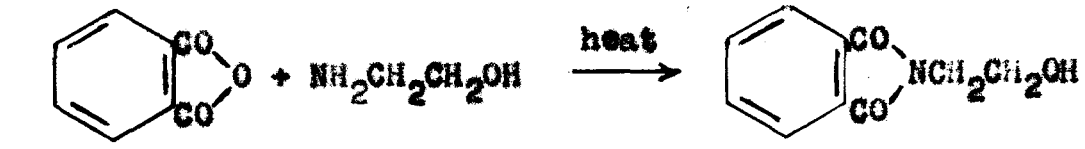


Fujii (289) in 1959 obtained glutamic acid by hydrolysis of the condensation product of glycine and acrylonitrile.

VIII. OXIDATION OF β-AMINO ALCOHOLS

(a) Oxidation of β-aminomonohydroxy alcohols

In 1943 Billman and Parker (290,291) synthesised glycine and alanine by the oxidation of the commercially available amino alcohols after the protection of the amino group by acylation. Thus glycine was prepared as follows:



In 1946 Billman (292) used commercially available β-benzoylaminopropyl alcohol for the synthesis of alanine.

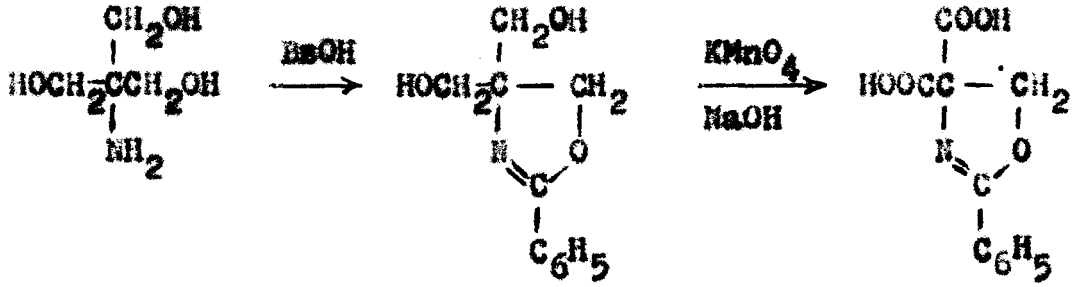
Billman and coworkers (293) in 1949 prepared glycine, alanine and α-aminobutyric acid from the corresponding amino alcohols by oxidation after converting the amino group into a substituted ammonium ion. Potassium permanganate was used for oxidation.

Glycine (294) was obtained in low yield when β-aminoethyl alcohol was heated with potassium hydroxide solution at a high temperature. But β-aminoethyl alcohol afforded 65%

yield of glycine (295) when it was heated with potassium hydroxide in presence of cadmium oxide at 160-185°.

(b) Oxidation of β-aminopolyhydroxy alcohols

In 1951 Billman and Parker (296) synthesised serine, and threonine from β-aminopolyhydroxy alcohols by an ingenious method of oxidation. Thus serine was prepared as follows:



Threonine was similarly synthesised.

(c) Oxidation of hydroxyamino acids

Klosterman and Painter (297) prepared aspartic acid in 40% over-all yield from γ-hydroxy-α-aminobutyric acid. The amino group was protected by benzoylation, oxidised to benzoylaspartic acid with potassium permanganate and finally debenzoylated to the free amino acid.

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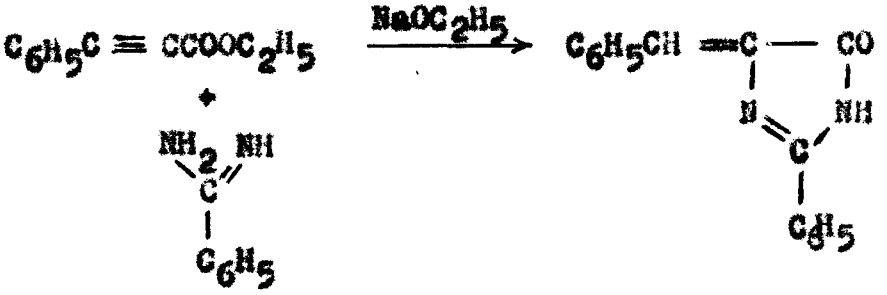
I N T R O D U C T I O N

INTRODUCTION

I: SYNTHESIS OF IMIDAZOLONES

Ruhemann and Cunnington (298) in 1889 prepared the first 5(4H)-imidazolone by the condensation of phenylpropiolic ethyl ester with benzamidine hydrochloride in the presence of sodium ethoxide and obtained 2-phenyl-4-benzylidene-5(4H)-imidazolone.



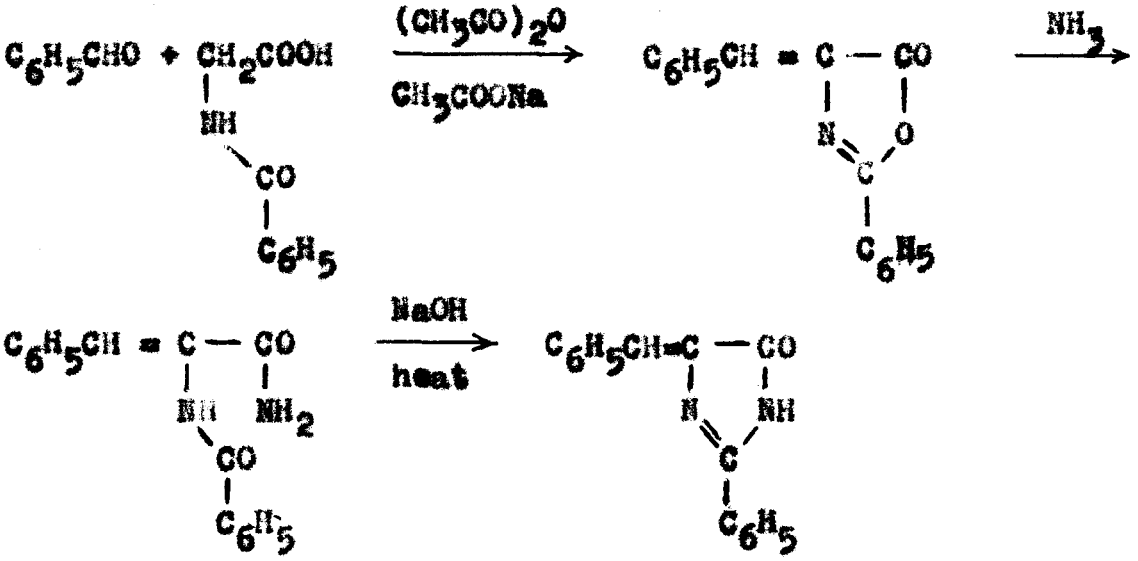
However, this method has not been used as a general method for the preparation of 5(4H)-imidazolones.

The following is a brief account of the various methods developed for the synthesis of 2,4-disubstituted 5(4H)-imidazolones.

(a) <u>Azlactone method</u>:

Erlenmeyer (299-303) prepared 2-phenyl-4-arylidene-5(4H)-imidazolones starting with azlactones. The synthesis of 2-phenyl-4-benzylidene-5(4H)-imidazolone (299,300) illustrates

this method. On heating a mixture of benzaldehyde and hippuric acid in the presence of fused sodium acetate and acetic anhydride the azlactone of α-benzoylaminocinnamic acid was formed. This azlactone readily afforded α-benzoylaminocinnamic acid amide on heating with concentrated ammonia in the presence of alcohol. The amide cyclized to give 2-phenyl-4-benzylidene-5(4H)-imidazolone under the influence of hot dilute sodium hydroxide solution.



The other imidazolones prepared by Erlenmeyer (301-303) using this method are 2-phenyl-4-anisylidene-5(4H)-imidazolone, 2-phenyl-4-furfurylidene-5(4H)-imidazolone etc.

In 1946, Williams and Ronzio (304) obtained very high yield of 2-phenyl-4-benzylidene-5(4H)-imidazolone from the corresponding azlactone on heating with aqueous alcoholic

ammonia followed by treatment with potassium carbonate.

In 1943 Cornforth and Huang (305) prepared 2-phenyl-4-benzylidene-,-anisylidene- and -furfurylidene-5(4H)-imidazolones by dissolving appropriate azlactones in dioxane by warming with aqueous ammonia followed by boiling with potassium hydroxide.

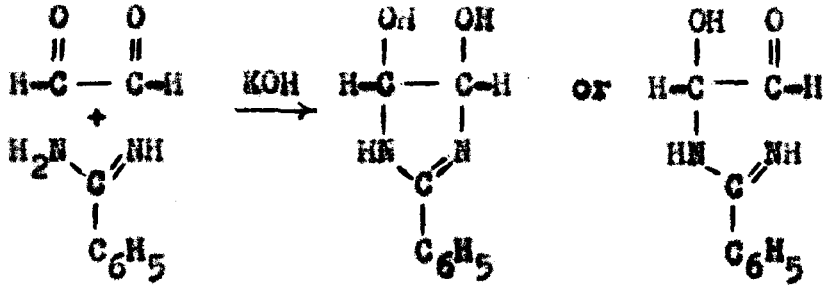
In 1953 Kjaer (306) employed azlactone method in the syntheses of 2-phenyl-4-isobutylidene-5(4H)-imidazolone and 2-methyl-4-benzylidene-5(4H)-imidazolone.

The acyl-α-amino acid amides do not undergo cyclisation to form the saturated 2,4-disubstituted 5(4H)-imidazolones on heating with alkali. They are hydrolysed to form the acylamino acids and ammonia (307). But the acyl derivatives of tertiary-α-amino acid amides are cyclised to form imidazolones (308,309) on similar treatments.

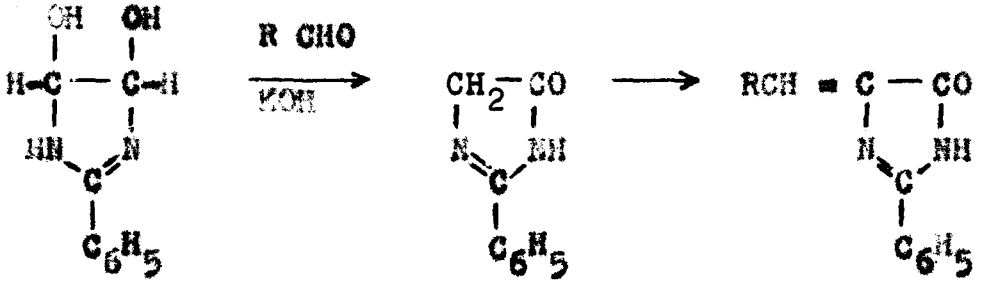
(b) <u>Benzamidine-glyoxal method</u>

In 1935, Ekeley and Ronzio (310) developed a method for the syntheses of 2-phenyl-4-arylidene-5(4H)-imidazolones by condensing benzamidine-glyoxal addition product with aromatic aldehydes. Actually, at that time, they thought that the condensation products obtained were either diaryl-pyrimidones (or hydroxypyrimidines) or 2-phenyl-4-aroyl-glyoxalines. On treating a mixture of glyoxal and benzamidine hydrochloride with potassium hydroxide a labile basic

substance is formed. It may be represented either as an open chain compound or preferably as a 2-phenyl-4,5-dihydroxy-2-imidazoline (benzamidine-glyoxal)(305).

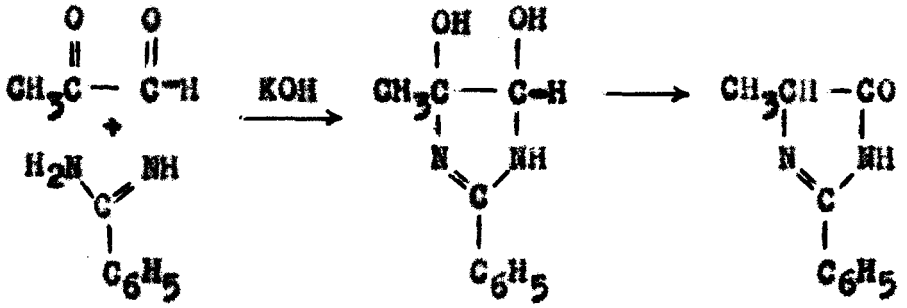


On condensing aromatic aldehydes with this substance in the presence of sodium or potassium hydroxide good yields of 2-phenyl-4-arylidene-5(4H)-imidazolones were obtained. The reaction may be formulated in the manner illustrated below using the more plausible 4,5-dihydroxy-2-imidazoline structure for the benzamidine-glyoxal complex. It is assumed that the dihydroxyimidazoline loses a molecule of water under the influence of the base to form 2-phenyl-5(4H)-imidazolone containing a highly reactive methylene group. The 2-phenyl-5(4H)-imidazolone thus formed readily undergoes condensation with aldehydes.



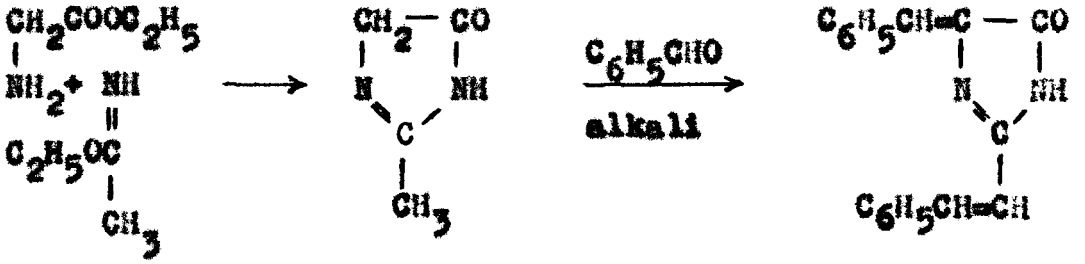
Numerous 2-phenyl-4-arylidene-5(4H)-imidazolones (310,311) were prepared by this method.

Saturated 2,4-disubstituted 5(4H)-imidazolones (305,312, 313) were prepared by the condensation of substituted glyoxal with amidine hydrochlorides. Thus 2-phenyl-4-methyl-5(4H)-imidazolone (305) was prepared by condensing methyl glyoxal with benzamidine hydrochloride in the presence of potassium hydroxide.

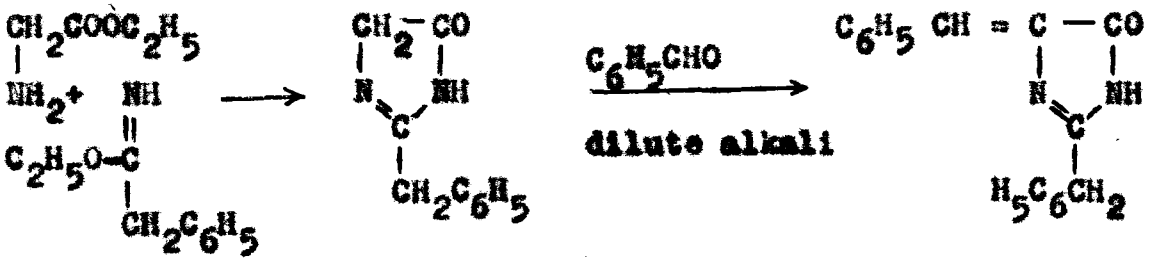


(c) <u>Imidic acid ester-glycine ester method:</u>

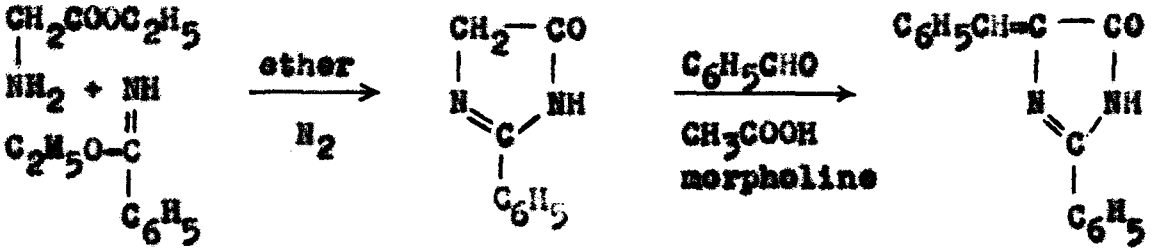
In 1907 Finger (314) obtained 2-methyl-5(4H)-imidazolone on condensing glycine ester with acetimidic acid ester at room temperature. 2-Methyl-5(4H)-imidazolone condensed with 2-moles of benzaldehyde to form 2-benzylidenemethyl-4-benzylidene-5(4H)-imidazolone.



Finger and Zeh (315) obtained 2-benzyl-5(4H)-imidazolone on condensing glycine ester with phenylacetimidic acid ester and the condensation product in turn afforded 2-benzyl-4-benzylidene-5(4H)-imidazolone when it was condensed with benzaldehyde in the presence of dilute alkali solution.

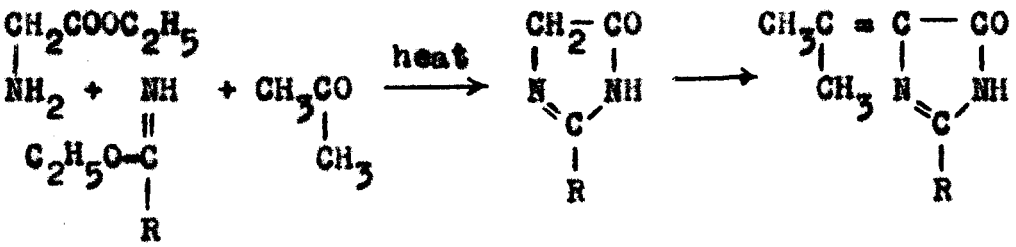


In 1953 Kjaer (316) prepared 2-phenyl-5(4H)-imidazolone in 18.8% yield by condensing benzimidic acid ester with glycine ester in the presence of anhydrous ether in nitrogen atmosphere. The product was purified by recrystallisation from benzene in an oxygen free atmosphere followed by sublimation. He obtained 2-phenyl-4-benzylidene-5(4H)-imidazolone in 77.4% yield on condensing 2-phenyl-5(4H)-imidazolone with benzaldehyde.



1-naphthaldehyde, furfural, isatin and pyruvic acid were also condensed with 2-phenyl-5(4H)-imidazolone.

In 1953, Lehr and collaborators (317,318) obtained 2-substituted 4-isopropylidene-5(4H)-imidazolones instead of the expected 2-substituted 5(4H)-imidazolones on condensing imidic acid esters with glycine ester using acetone as solvent. Glycine ester and imidic acid ester first condense to form-2-substituted 5(4H)-imidazolone which in turn reacts with acetone to form 2-substituted 4-isopropylidene-5(4H)-imidazolone.



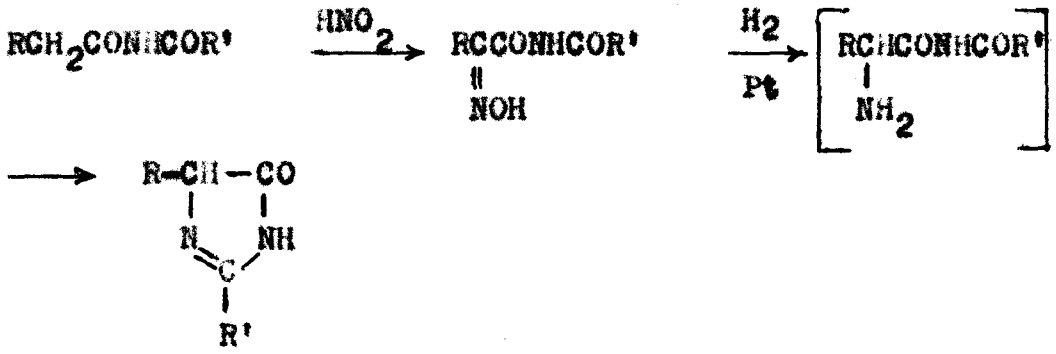
Lehr and coworkers (317-319) prepared a large number of 2,4-disubstituted 5(4H)-imidazolones by refluxing aliphatic and hydroaromatic ketones, acetoacetic ester, levulinic ester and acetophenone with a mixture of an imidic acid ester and glycine ester. In the case of high boiling ketones benzene was used as solvent while in the case of low boiling ketones excess of ketones themselves were the solvents. The structure of these compounds was confirmed by synthesising one of them namely 2-benzyl-4-cyclohexylidene-5(4H)-imidazolone by simultaneous reaction of phenylacetimidic acid ester, glycine ester and cyclohexanone and also by the condensation of the preformed 2-benzyl-5(4H)-imidazolone

with cyclohexanone.

Saturated 2,4-disubstituted 5(4H)-imidazolones (305,309) were obtained when amino acid esters were condensed with benzimidic acid ester. 2-phenyl-4-methyl-5(4H)-imidazolone (305) and 2-phenyl-4,4-dimethyl-5(4H)-imidazolones (309) are the only saturated imidazolones prepared by this method.

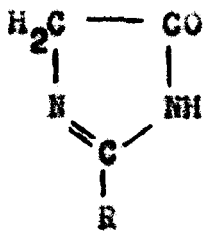
(d) Diacylamine method

Shaw in 1955 (320) reported a new synthesis of saturated 5(4H)-imidazolones involving the spontaneous cyclization of α-aminoacyl amines by the following procedure.

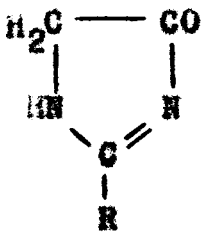


II STRUCTURE AND PROPERTIES

Numbering of the imidazolone ring is based on the imino hydrogen which may have two alternative positions as indicated in the formulae.



5-imidazolone

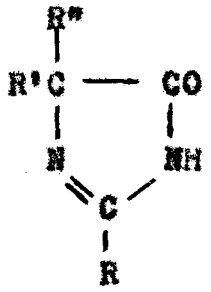


4-imidazolone

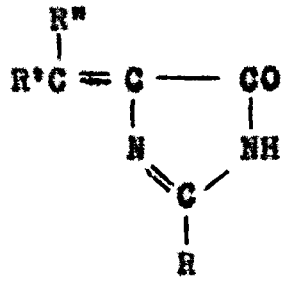
Because of this, 5-imidazolones cannot be distinguished from 4-imidazolones and therefore in the literature these compounds have been referred to as 5(4H)-imidazolones as well as 4(5H)-imidazolones. In the present discussion the nomenclature 5(4H)-imidazolone has been preferred.

2,4-Disubstituted 5(4H)-imidazolones (or, 2,5-disubstituted 4(5H)-imidazolones)are also known as 2,4-disubstituted 2-imidazoline-5-ones and 2,4-disubstituted 5-ketodihydroglyoxalines.

5(4H)-imidazolones may be classified into two groups, saturated and unsaturated since the two types possess characteristic differences in properties.

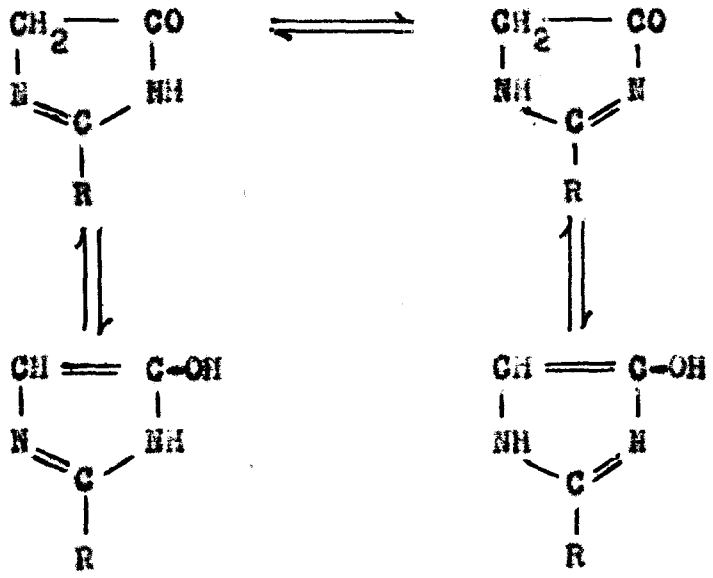


Saturated
5(4H)-imidazolones



Unsaturated
5(4)-imidazolones

The 5(4H)-imidazolones possess an amidine and a keto-enol system in the molecule and therefore, in addition to many resonance contributions, four tautomeric forms are possible.

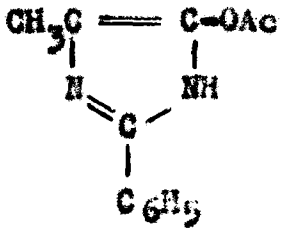


Evidence for the existence of the imidazolone as well as the hydroxyimidazole forms is available in the chemical behaviour of this class of compounds. The enolic forms give dibenzoyl derivatives (314,315) which are obtained

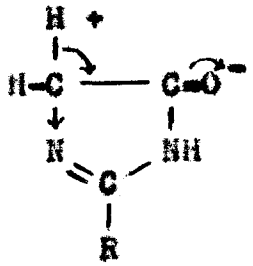
when 2-methyl-5(4H)-imidazolone or 2-benzyl-5(4H)-imidazolone are treated with benzoyl chloride in pyridine.

R= CH_3- or $C_6H_5CH_2$-

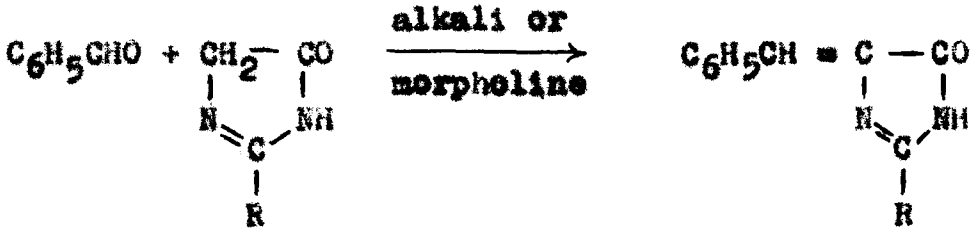
Similarly, Cornforth and Huang (305) obtained the acetyl derivative of 2-phenyl-4-methyl-5(4H)-imidazolone with basic properties which can be explained if it is considered to be an O-acetyl derivative of the hydroxy-imidazole.



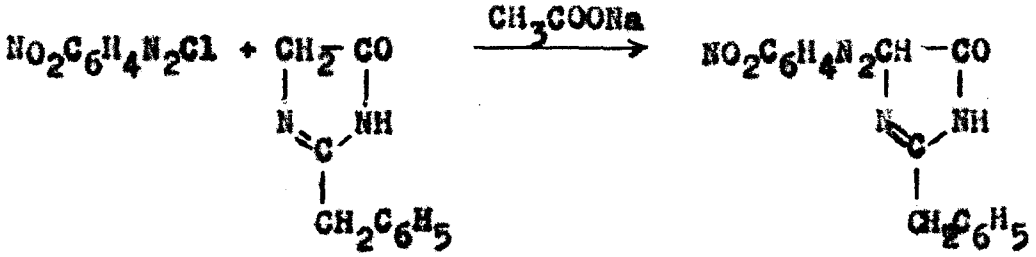
The highly reactive character of the methylene group can be explained only in terms of the keto form in which the carbonyl group acts as an electron attracting group along with the nitrogen-carbon double bond which forms the other flank of the methylene group.



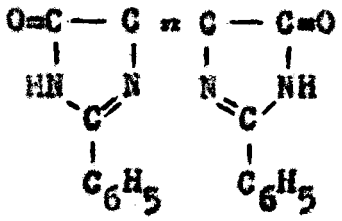
The methylene group is so active that under even very mild conditions it undergoes condensation with aldehydes as reported by Finger and Zeh (314,315) and Kjaer (316) and also with ketones which has been extensively studied by Lehr and collaborators (317-319)

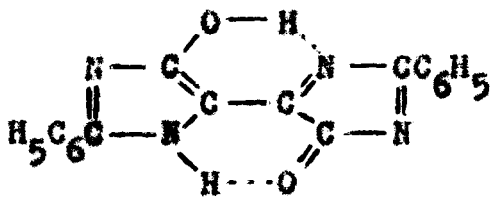


Finger and Zeh (314,315) also recorded coupling of the methylene group with the aromatic diazonium compounds.



In fact, the methylene group in 2-phenyl-5(4H)-imidazolone is so active that it spontaneously undergoes oxidation with atmospheric oxygen to form the intensely red coloured substance "glyoxaline red" (314,316). Glyoxaline red was first prepared by Ruhemann and Stapleton (321) by condensing acetylene dicarboxylic ester with benzamidine hydrochloride. The following two different structures (321,322,316) have been proposed for glyoxaline red.

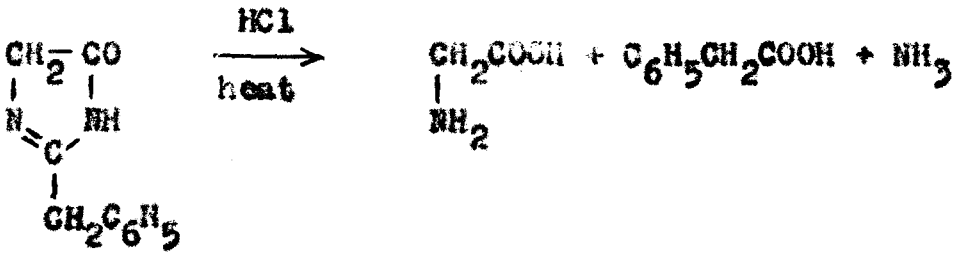




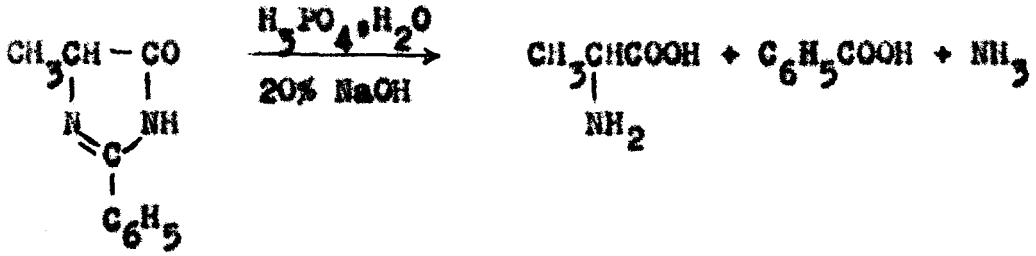
The 5(4H)-imidazolones are amphoteric compounds which form salts with acids as well as bases. 2-Phenyl-4-methyl-5(4H)-imidazolone forms a silver salt when treated with silver nitrate and also forms a sparingly soluble picrate (305). Lehr and coworkers (317) obtained hydrochlorides of the unsaturated imidazolones by dissolving them in absolute ethanol and saturating the solutions with dry hydrogen chloride. Therefore, it may be concluded that the basic characteristics are due to the amidine part of the molecule while the acidic properties are concerned with the enolic hydrogen.

The unsaturated 4-arylidene-5(4H)-imidazolones are quite stable compounds and are not affected by dilute acids or alkalies. They can easily be subjected to ordinary heating and crystallized from boiling alcohol or acetic acid (298) without undergoing decomposition. These unsaturated imidazolones can also be stored for long periods of time without decomposition. But the unsaturated 4-alkylidene-5(4H)-imidazolones are less stable.

However, 5(4H)-imidazolones with hydrogen at 4-position are quite unstable. They even decompose when allowed to stand and are unstable to heat. They undergo hydrolysis when heated with acids or alkalies or even with water. Finger and Zen (315) hydrolysed 2-benzyl-5(4H)-imidazolone to phenylacetic acid, ammonia and glycine.

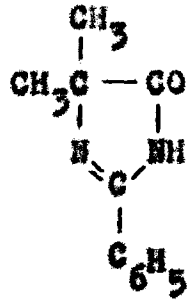


Similarly, Cornforth and Huang (305) hydrolysed 2-phenyl-4-methyl-5(4H)-imidazolone with phosphoric acid or 20% sodium hydroxide solution and detected the presence of alanine in the hydrolysate by the ninhydrin test.



2-Benzyl-5(4H)-imidazolone was hydrolysed to phenylacetylglycine amide (315,323) on boiling with water.

It is of interest to note that saturated 5(4H)-imidazolones, differ considerably in their stability depending upon the number of hydrogen atoms present at 4-position. Some idea about the relative stability of the saturated-5(4H)-imidazolones may be obtained from the following facts. Treatment with dilute sodium hydroxide converts α-benzoylaminoisobutyric acid amide into 2-phenyl-4,4-dimethyl-5(4H)-imidazolone (308) while similar treatment of the amides of benzoylalanine and benzoylglycine leads to hydrolysis of the amide linkage (307). However, 2-phenyl-4-methyl-5(4H)-imidazolone (305) can be synthesised by other methods but it is not as stable as 2-phenyl-4,4-dimethyl-5(4H)-imidazolone. On the other hand 2-phenyl-5(4H)-imidazolone is far more unstable and undergoes spontaneous oxidation by atmospheric oxygen to give "glyoxaline red." (314,316).

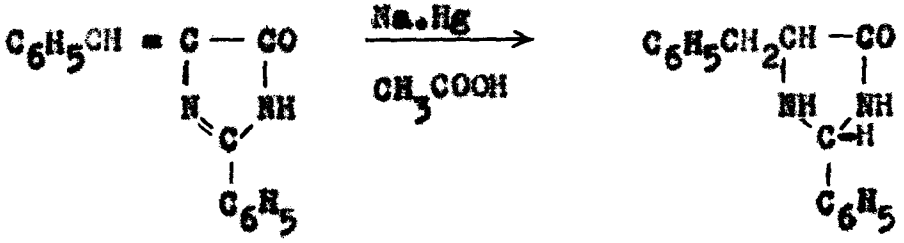


2-Phenyl-4,4-dimethyl-5(4H)-imidazolone.

2-Phenyl-4-methyl-5(4H)-imidazolone.

2-Phenyl-5(4H)-imidazolone

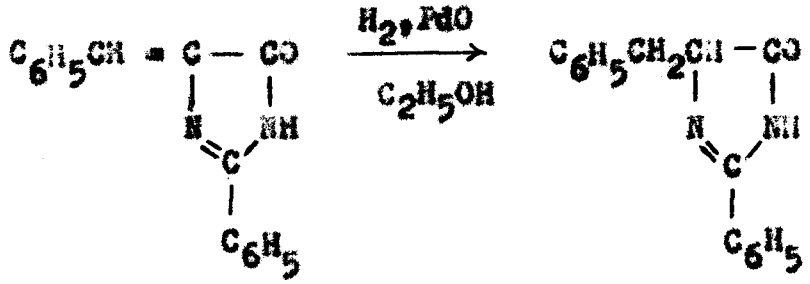
Granacher and Gulbas (324) in 1927 and Williams and coworkers (325) in 1945 indicated that 4-arylidene-5(4H)-imidazolones can be reduced catalytically as well as with sodium amalgam in acetic acid so that both the exocylic and the ring double bonds were saturated.



Granacher and coworker (324) also succeeded in hydrlysing this imidazolidone to phenylalanine, phenylalanine amide and benzaldehyde using hydrochloric acid.

Kjaer (306) in 1953 using palladium as catalyst reduced only the exocyclic double bond of the 4-arylidene-5(4H)-imidazolone and noted the unstability of the dihydroderivative but he did not present any chemical

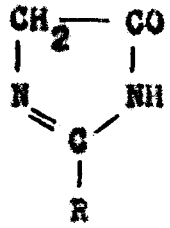
evidence for the exclusive reduction of the exocyclic double bond nor he reported yield of the reduction product obtained.

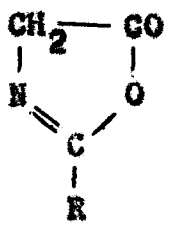


In 1957 Brenner and coworkers (326) carried out the hydrogenation of the exocyclic double bond of 2-(2-hydroxyphenyl)-4-benzylidene-5(4H)-imidazolone using Pd (C) in the presence of acetone as solvent to establish the structure of a by-product obtained in their studies on "aminoacyl incorporation." They also did not report yield of the hydrogenation product.

III: IMIDAZOLONE SYNTHESIS OF AMINO ACIDS

A close study of the foregoing discussion on structural characteristics and chemical behaviour of the 5(4H)-imidazolones reveals certain interesting features which are in common with azlactones, the oxygen analogues of the imidazolones which may also be considered as azlactams.

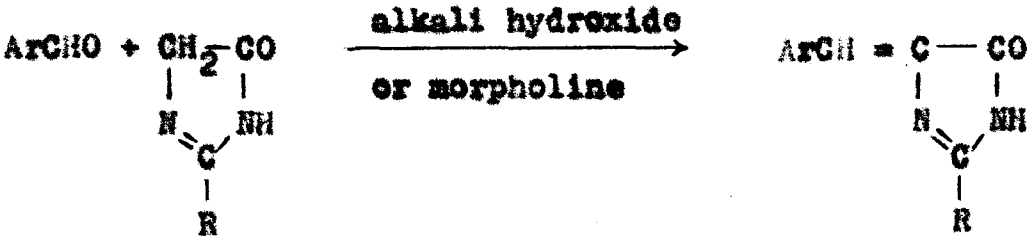




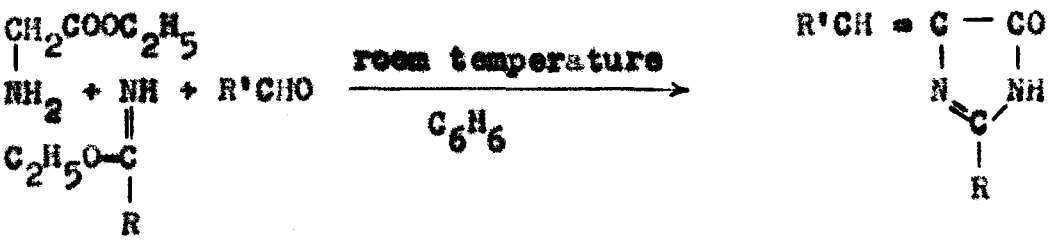
The most important characteristic of both the classes of compound is the presence of an active methylene group which readily undergoes condensation reactions of the aldol type. In both the cases methylene group is activated by the two unsaturated groups flanking it. In the case of azlactones Erlenmeyer (124-127,327) took full advantage of this characteristic in developing a general method for the syntheses of α-amino acids, α-keto acids and related compounds and today it is one of the most useful methods for this purpose.

In view of these considerations it was thought to be worthwhile to examine the possibility if 5(4H)-imidazolones could be used as intermediates in the syntheses of amino acids and thus a new method could be developed which may, perhaps, have certain advantages over the azlactone and other methods of amino acids syntheses.

The 5(4H)-imidazolones undergo condensation with benzaldehyde and other aromatic aldehydes most readily in the presence of alkali hydroxide or morpholine giving high yields of unsaturated 4-arylidene-5(4H)-imidazolones(314-316).



In the present work it has further been found that the unsaturated imidazolones are obtained in very high yields by simply allowing to stand at room temperature a mixture of glycine ester, an imidic acid ester and an aldehyde with or without a solvent and even without the use of a catalyst since the basic reactants may themselves act as catalyst.



The very high yields of the 4-arylidene-5(4H)-imidazolones and the ease and simplicity of the reaction made it a very attractive proposition to further examine the possibility of the use of unsaturated imidazolones as intermediates in the syntheses of amino acids.

It may be pointed out that the conditions of azlactone synthesis are drastic as comparing to the mild conditions of imidazolone synthesis. The yields of imidazolones are favourably comparable with t ose of the corresponding azlactones as indicated in Table I.

The imidazolone synthesis has got another advantage over the azlactone synthesis in regard to the fact that 5(4H)-imidazolones can be condensed with a variety of ketones (317-319) while the hippuric acid azlactone has so far been condensed only with acetone (332) and methyl ethyl ketone (333) in comparatively low yields.

The unsaturated imidazolones are comparatively more stable compounds than the corresponding azlactones and therefore they can be crystallized and purified more conveniently. The imidazolones can be kept without decomposition for a long period of time.

In the present work unsaturated imidazolones have been successfully reduced catalytically to the corresponding

TABLE I

A Comparison of the yields obtained of unsaturated imidazolones with those of unsaturated azlactones reported in the literature

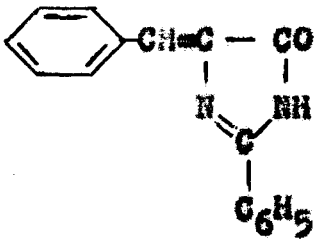
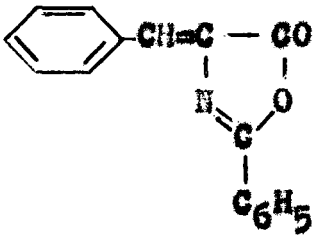
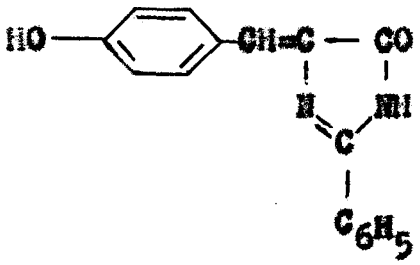
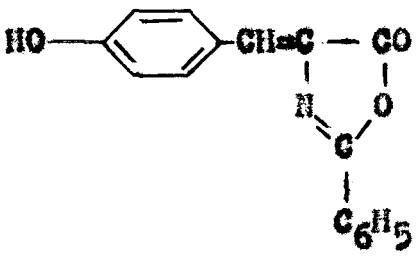
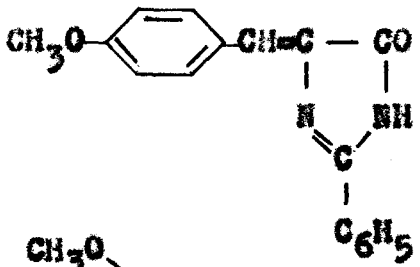
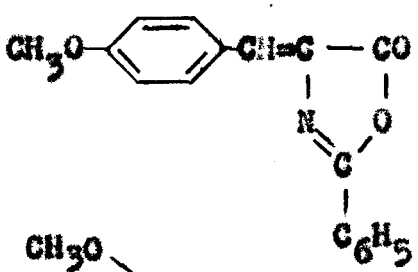
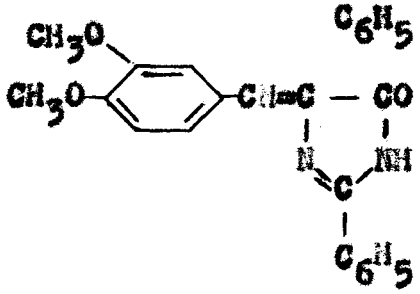
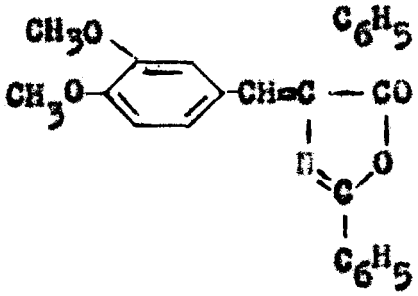
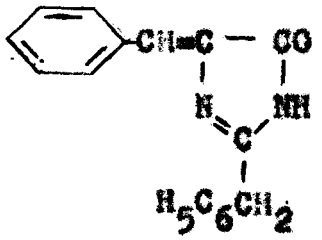
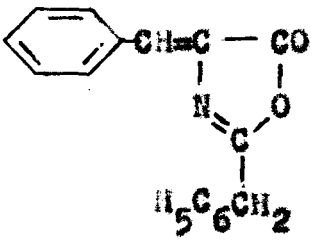
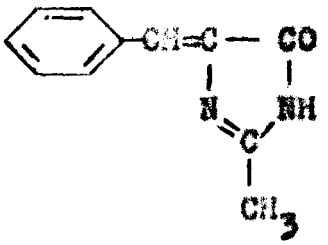
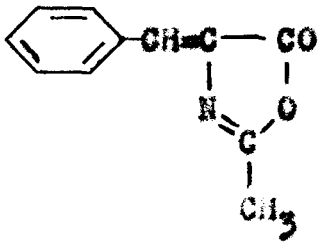
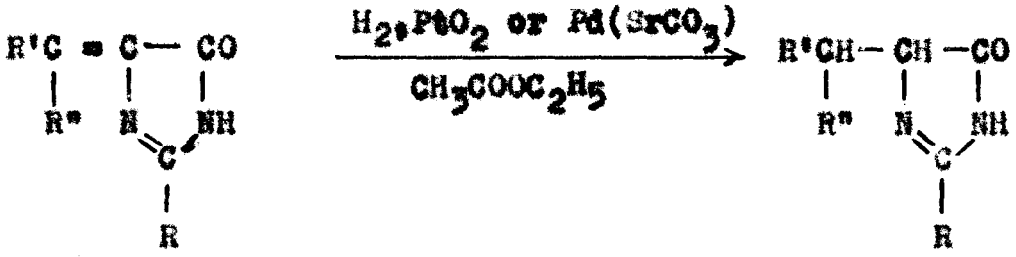
Imidazolone		Azlactone		
Structural formula	yield	Structural formula	yield	Ref.
	76%		64% 80%	137 127
	86%		85%	126
	85%		80%	328
	88%		71%	329

TABLE I (continued)

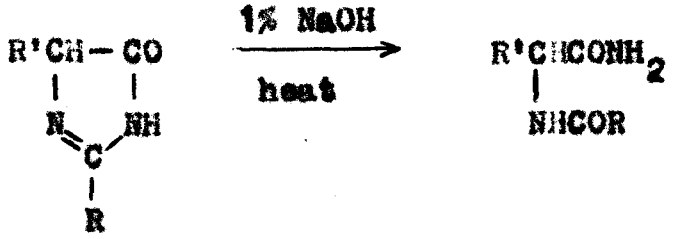
Imidazolone		Azlactone		
Structural formula	yield	Structural formula	yield	Ref.
	46 %		37 %	330
	28 %		75 %	331

dihydro derivatives by the addition of hydrogen to the exocyclic double bond.

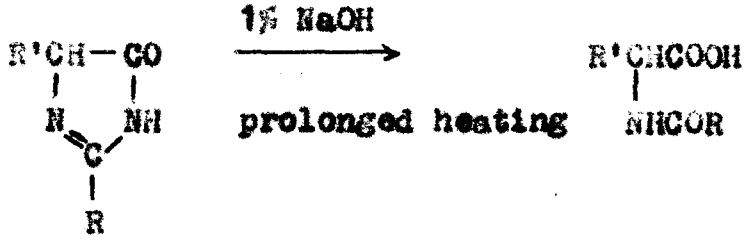


The saturated imidazolones thus obtained have been found to be unstable and undergo alkaline hydrolysis readily.

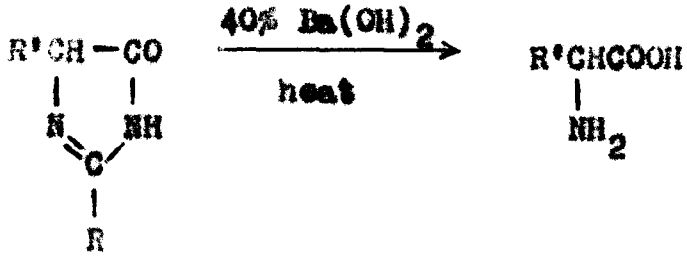
When heated with 1% sodium hydroxide solution the saturated imidazolones are hydrolysed to the corresponding acylamino acid amides.



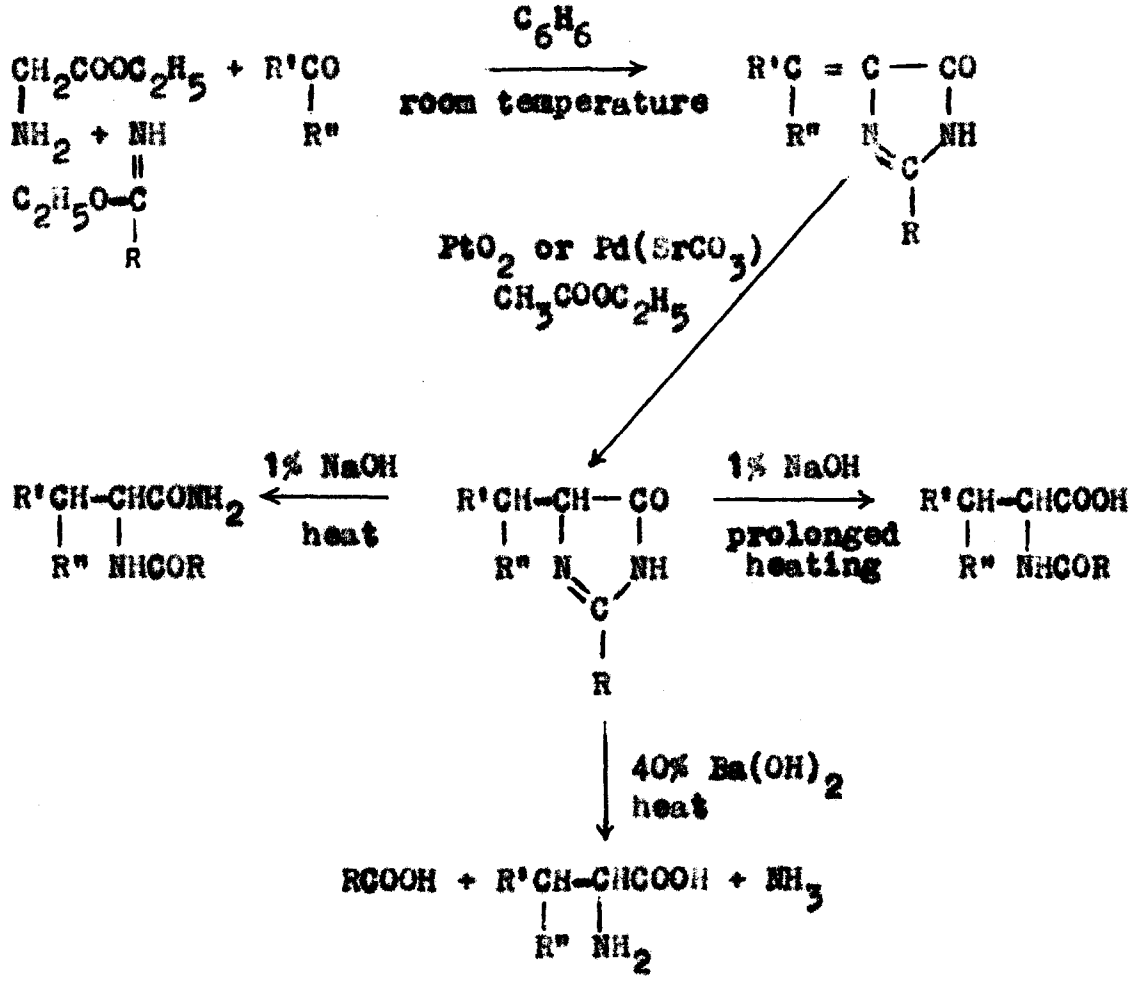
The saturated imidazolones afford α-acylamino acids on prolonged heating with 1% sodium hydroxide solution.



If the saturated imidazolones are subjected to hydrolysis with 40% barium hydroxide solution amino acids are obtained.



The following chart summarises all the reactions involved in the syntheses of α-amino acids and their derivatives.



R= C_6H_5-, $C_6H_5CH_2$- or CH_3-; R'= aryl or alkyl; R"= H or alkyl

Thus, according to the expectations, the imidazolones can be used as intermediates in the synthesis of amino acids and their derivatives and, therefore, it provides an entirely new method for this purpose which has certain advantages over the azlactone method as indicated above and appears to be full of potential to be developed into a general method for the syntheses of amino acids. It would not be surprising if, at least, for the syntheses of some

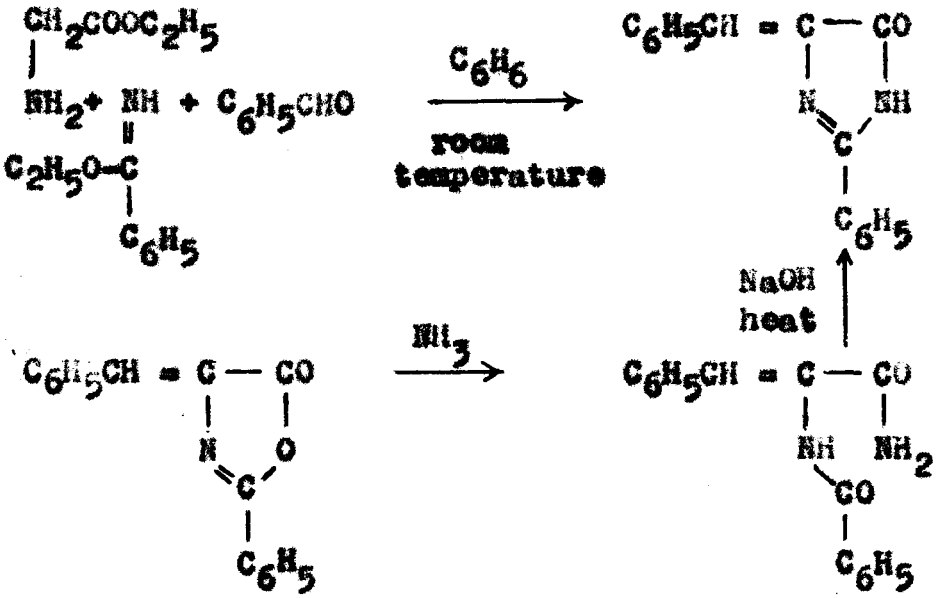
of the amino acids this new method proves to be more convenient and useful.

The imidazolone synthesis also compares favourably with the azlactone synthesis of amino acids from the point of view of the availability of the starting materials. Glycine ethyl ester can, perhaps, be as conveniently available as glycine itself from methyleneaminoacetonitrile (96,105). Benzonitrile has become available in sufficient quantities from benzenediazonium chloride through the Sandmeyer reaction. The benzonitrile can be converted into benzimidic acid ethyl ester in almost quantitative yield and it can directly be used for the syntheses of unsaturated imidazolones. In the case of azlactone synthesis glycine has to be converted into hippuric acid before it could be used in the reaction.

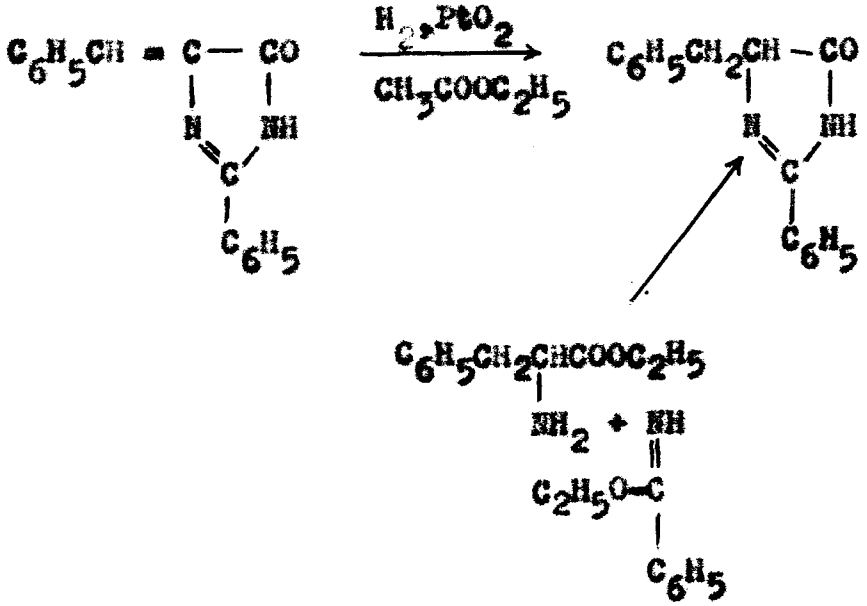
As an example synthesis of dl-phenylalanine and its derivatives through imidazolones is outlined below to show the success of this method.

When benzaldehyde was allowed to stand with a mixture of glycine ethyl ester and benzimidic acid ethyl ester in the presence of benzene at room temperature for 20 hours 2-phenyl-4-benzylidene-5(4H)-imidazolone was obtained in 76.3% yield. The product was identified by determining

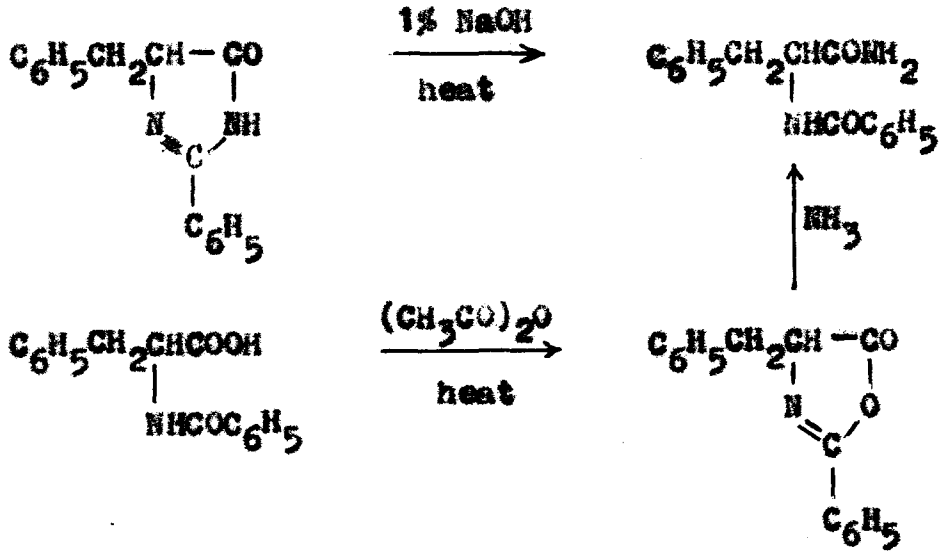
the mixed melting point with an authentic sample of the compound by the azlactone method (299,300) and by comparing the infra red spectra of these two samples.



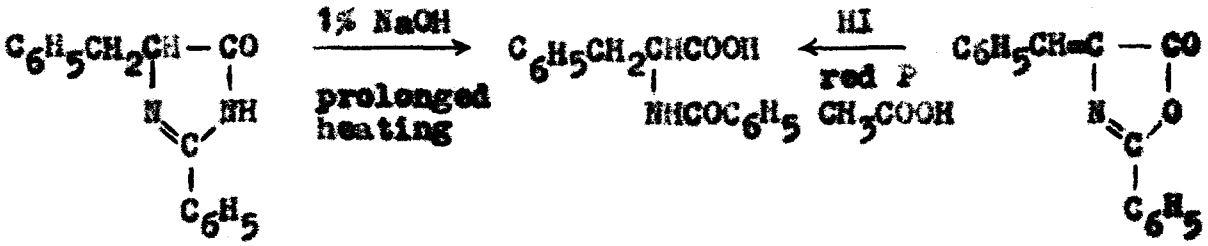
The unsaturated 2-phenyl-4-benzylidene-5(4H)-imidazolone was subjected to hydrogenation using platinum oxide catalyst in the presence of ethyl acetate. The absorption of hydrogen was practically ceased when the substance absorbed one molecular proportion of hydrogen. The yield of 2-phenyl-4-benzyl-5(4H)-imidazolone was 84.1%. Structure of this compound was established by an unambigous synthesis of the compound using the method by which Cornforth and Huang (305) synthesised 2-phenyl-4-methyl-5(4H)-imidazolone.



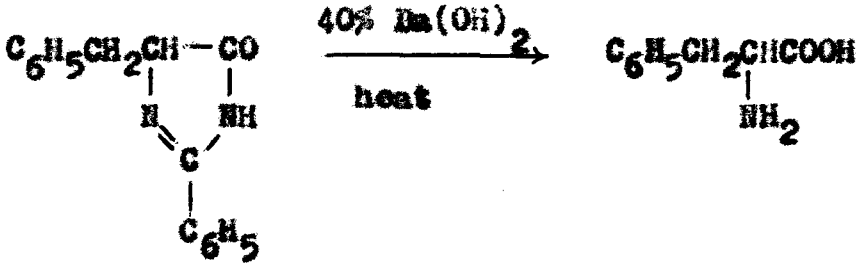
The saturated 2-phenyl-4-benzyl-5(4H)-imidazolone on refluxing with 1% sodium hydroxide solution for 15 minutes yielded 26.6% dl-N-benzoylphenylalanine amide which was identified by determining the mixed melting point with a sample synthesised by azlactone method (334) and by comparing the infra red spectra of these two samples.



dl-N-Benzoylphenylalanine was obtained in 68.5% yield when the 2-phenyl-4-benzyl-5(4H)-imidazolone was refluxed with 1% sodium hydroxide solution for two hours. The product was identified by taking mixed melting point with a sample prepared by the azlactone method (138) and by comparing infra red spectra of the two samples.

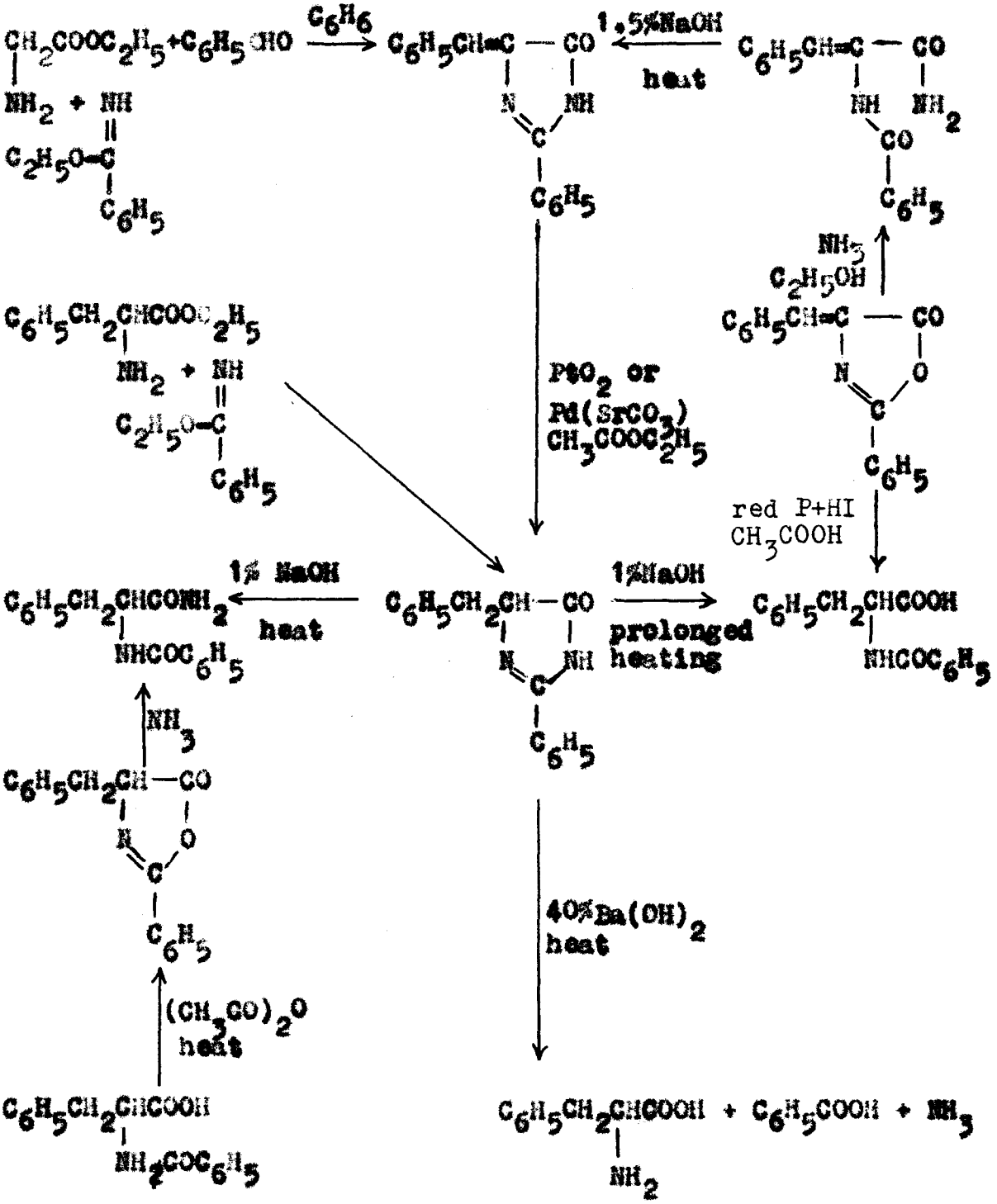


The 2-phenyl-4-benzyl-5(4H)-imidazolone could also be converted into dl-phenylalanine in 67.9% yield by refluxing with about 5 molecular proportions of a 40% barium hydroxide solution for 7.5 hours. The phenylalanine obtained was identified by determining its mixed melting point with an authentic sample and by comparing the infra red spectra of these two samples.



The following chart summarises all the reactions

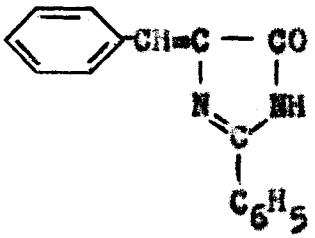
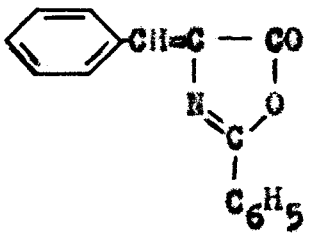
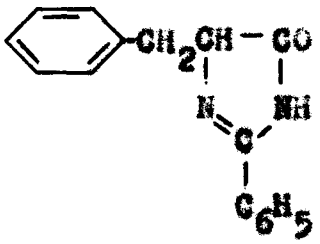
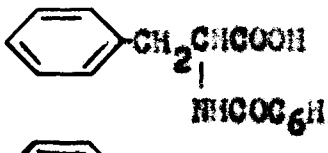
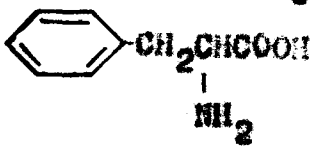
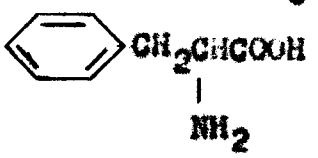
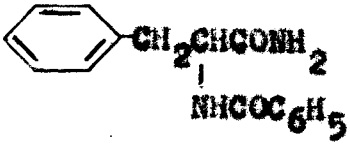
involved in the syntheses of phenylalanine and its derivatives.



The above synthesis of phenylalanine provides a very interesting case for the comparison of the azlactone (137, 138) and the imidazolone methods of syntheses of amino acids.

TABLE II

A comparison of imidazolone and azlactone methods of syntheses of phenylalanine and its derivatives

Imidazolone method		Azlactone method		
Product	yield*	Product	yield*	Ref.
	76.3%		63%	137
	64.2%			
	44%		45.4%	138
	43.6%		41%	137
	17.1%			

* Over-all yields based on benzaldehyde used.

From Table II it is quite clear that the imidazolone method is quite favourably comparable with the azlactone syntheses of phenylalanine and its derivatives. It has got the added advantage of the ease and simplicity of the reaction and purity and stability of the intermediates. Moreover, the catalytic reduction of unsaturated imidazolone followed by the hydrolysis of the reduction product to dl-phenylalanine provides, perhaps, a more economical and simpler process as compared to the azlactone synthesis (137) in which a mixture of hydroiodic acid and red phosphorous in presence of acetic anhydride is used for the reduction and hydrolysis of the unsaturated azlactone.

In view of the successful synthesis of phenylalanine by the imidazolone method it was considered worthwhile to extend this method for the synthesis of other amino acids and related compounds and therefore systematic studies were undertaken with the following objectives.

1. Improvement of the imidazolone synthesis in order to work out the optimum conditions for getting the best yield of imidazolones.
2. Reduction of the exocylic double bond of the unsaturated imidazolones.
3. Hydrolysis of saturated imidazolones to the corresponding

amino acids, acylamino acids and acylamino acid amides.

These studies led to very interesting results which made it possible to suggest that the imidazolone method could be used as a new method for the synthesis of amino acids and their derivatives and appears to be full of potential to be developed into a general method for the synthesis of amino acids with, at least, as much scope as that of azlactone method. It is, however, necessary that many more amino acids should be synthesised by this method before it is established and accepted as a general method. Therefore, the main object of the present work was to work out the details of procedures and scope of the proposed imidazolone synthesis of amino acids, the details of which are fully discussed in the following pages. These procedures can be used for the syntheses of other amino acids.

D I S C U S S I O N

DISCUSSION

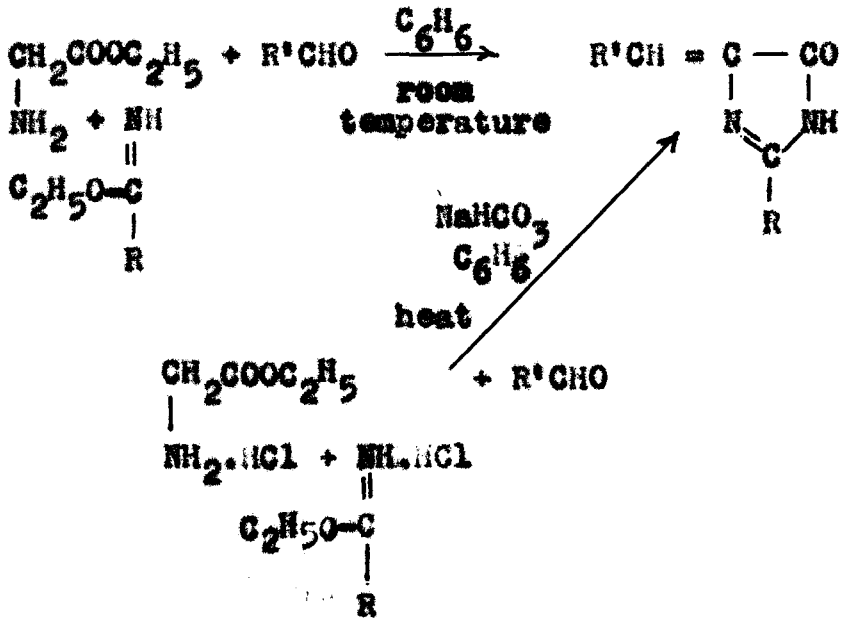
I SYNTHESIS OF UNSATURATED 2,4-DISUBSTITUTED 5(4H)-IMIDAZOLONES

If 2,4-disubstituted 5(4H)-imidazolones are to be used as intermediates in the synthesis of amino acids then success of this method would depends upon the ease with which unsaturated imidazolones could be obtained in high yields. Ruhemann and Cunnington's (298) benzamidine-propiolic ester method has been used for the synthesis of only 2-phenyl-4-benzylidene-5(4H)-imidazolone. Erlenmeyer's (299-306) azlactone method is a very useful method for the syntheses of imidazolones but there would be no advantage of the imidazolone synthesis of amino acids if the imidazolones were to be obtained from the azlactones which themselves can be directly converted into amino acids. Ekeley and Ronzio's (310,311) benzamidine-glyoxal method requires glyoxal and benzamidine hydrochloride which are not so readily available starting materials. Moreover, this process involves two steps and the yields are not very good. For example, the yields of 2-phenyl-4-benzylidene-5(4H)-imidazolone was only 49.2% and that of 2-phenyl-4-anisylidene-5(4H)-imidazolone was only 20.5%. Finger's (314-316) imidic acid ester - glycine ester method does not give satisfactory

yields because the unsubstituted imidazolone is highly unstable and is obtained in very low yield. Lehr's (317-319) method is an improvement of Finger's method which does not require isolation of the intermediate. They have used this method for the preparation of a large number of condensation products of ketones. However, it is only in three cases the yields have been reported and these yields are low. Therefofe, no idea can be formed about the success of the process as a preparative method giving high yields. Moreover, they did not use aldehydes in their condensation reaction.

From the above discussion it would appear that the available methods for the syntheses of unsaturated imidazolones are far from satisfactory as preparative methods and if imidazolones are to be used as intermediates in the synthesis of amino acids, improvement of the available methods or development of a new method to get high yields of imidazolones is very necessary. In view of these considerations Finger's method as modified by Lehr and coworkers (317-319) which involves heating of a mixture of a ketone, an imidic acid ester and glycine ester was extended to the use of aldehydes and intensively studied to get high yields. A modification of this method was also developed in which the carbonyl compound could be condensed with the

hydrochlorides of imidic acid ester and glycine ester in the presence of sodium bicarbonate.



(a) Method I:

A number of experiments were carried out to find out the optimum conditions for the condensation of aldehydes with a mixture of an imidic acid ester and glycine ester and it was observed that the aldehydes condense very smoothly at the room temperature. However, the ketones were condensed at higher temperatures according to Lehr and coworkers (317). Table III gives an account of the unsaturated imidazolones prepared in connection with the present work.

Procedure: The imidazolones were prepared by allowing to stand a mixture of an aldehyde, an imidic acid ester and

TABLE III

Unsaturated imidazolones obtained by the condensation of carbonyl compounds with a mixture of glycine ester and imidic acid esters

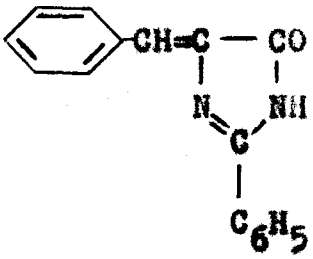
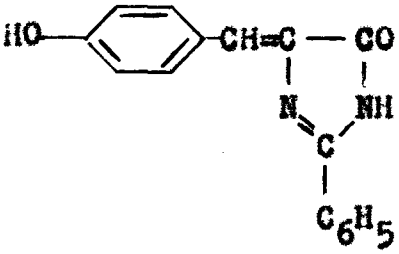
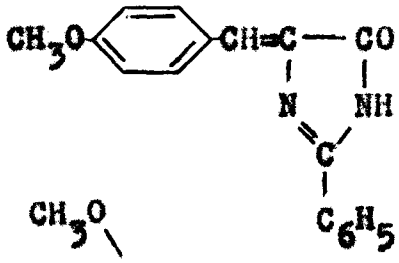
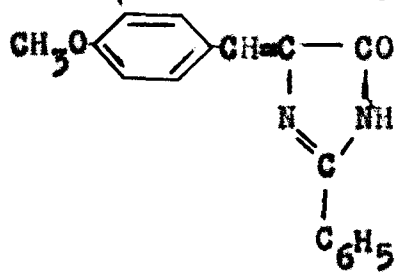
Name	Structural formula	yield
2-Phenyl-4-benzylidene-5(4H)-imidazolone.		76.3%
2-Phenyl-4-(p-hydroxy-benzylidene)-5(4H)-imidazolone.		85.6%
2-Phenyl-4-anisylidene-5(4H)-imidazolone		85.2%
2-Phenyl-4-(3,4-dimethoxy-benzylidene)-5(4H)-imidazolone.		87.8%

TABLE III (continued)

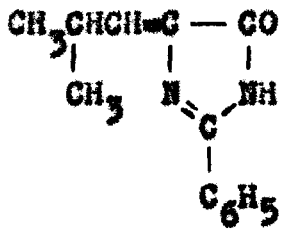
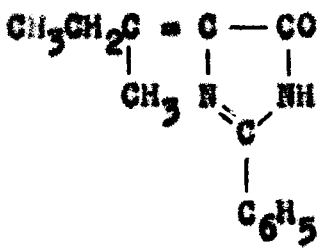
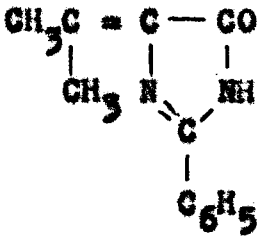
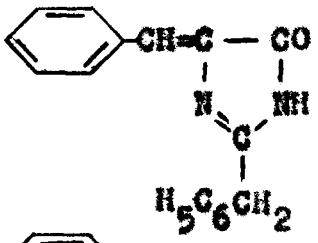
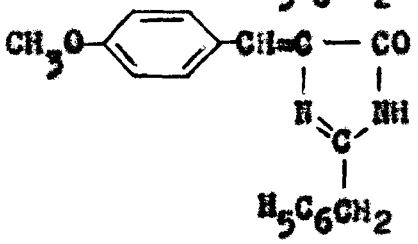
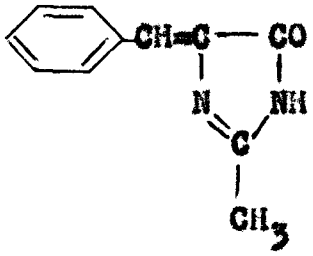
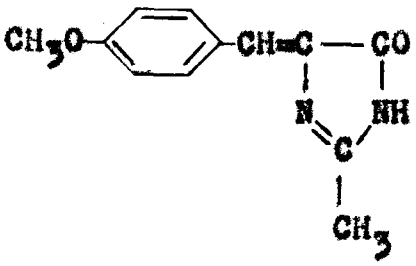
Name	Structural formula	yield
2-Phenyl-4-isobutylidene-5(4H)-imidazolone.		55.6%
2-Phenyl-4-sec-butylidene-5(4H)-imidazolone.		49.7%
2-Phenyl-4-isopropylidene-5(4H)-imidazolone.		64.2%
2-Benzyl-4-benzylidene-5(4H)-imidazolone.		46.4%
2-Benzyl-4-anisylidene-5(4H)-imidazolone.		48.7%

TABLE III (continued)

Name	Structural formula	Yield
2-Methyl-4-benzylidene-5(4H)-imidazolone.		14.7%
2-Methyl-4-anisylidene-5(4H)-imidazolone.		57.3%

glycine ester taken in the ratio of 1:1.15:1.2 in the presence of benzene at room temperature for 20-24 hours in a tightly stoppered Erlenmeyer flask. The mixture was occasionally shaken till the imidazolone began to separate in 0.5-4 hours. In most cases the mixture was completely solidified into an yellow mass of product. The yellow 2-phenyl-4-arylidene-5(4H)-imidazolones became slightly red coloured by the end of the reaction and the red colour became more intense when the flask was opened, due to the atmospheric oxidation of the unreacted 2-phenyl-5(4H)-

imidazolone to glyoxaline red. The product was heated with alcohol, filtered hot and washed thoroughly with alcohol.

The condensation of benzaldehyde was particularly studied under different conditions in order to find out the optimum conditions for the reaction and the important observations were recorded. Instead of benzene, toluene or xylene could also be used as solvent without any difference in yield. Even when no solvent was used the yield was practically the same but with the disadvantage that the product obtained was a hard solid mass which was difficult to remove from the flask. The reaction could also be carried out by heating the mixture of the reactants for one hour on a water bath at 70° but the yield was about 3% less. When all the three reactants were used in equimolecular proportions the yield was only 56.6% as compared to 76.3% when benzaldehyde, benzimidic acid ester and glycine ester were used in the ratio of 1:1.13:1.17.

However, for the condensation of Ketones it was found that the procedure recommended by Lehr and coworkers (317) was quite satisfactory. In the present work acetone and methyl ethyl ketone were condensed. When a mixture of equimolecular amounts of benzimidic acid ester and glycine ester was refluxed with a very large excess of acetone for 7.5 hours, 64.2% yield of 2-phenyl-4-isopropylidene-5(4H)-

imidazolone was obtained. In the case of methyl ethyl ketone a mixture of equimolecular proportions of benzimidic acid ester and glycine ester and a little excess of the ketone was refluxed in benzene for 5 hours, when 2-phenyl-4-sec-butylidene-5(4H)-imidazolone was obtained in 49.7% yield.

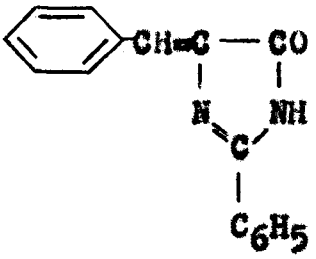
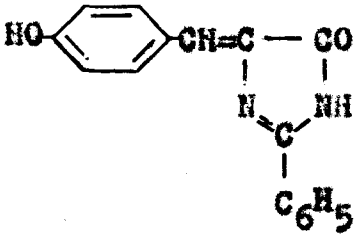
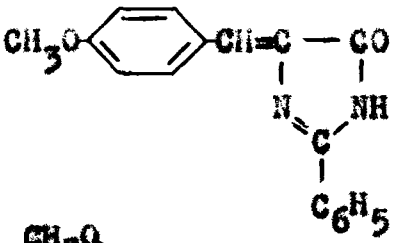
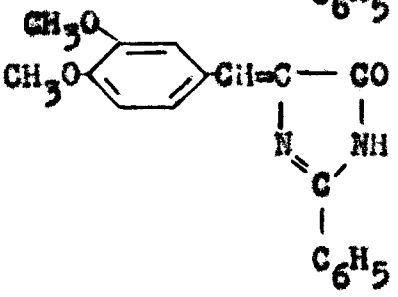
(b) Method II:

Since the unsaturated imidazolones are readily formed on merely allowing a mixture of an aldehyde, an imidic acid ester and glycine ester to stand at room temperature it was considered worthwhile to examine the possibility of the reaction to be carried out by using the hydrochlorides of the imidic acid ester and glycine ester in the presence of a weak alkali such as sodium bicarbonate so that the imidic acid ester and glycine ester are liberated during the reaction. Such a procedure would avoid the pre-conversion of the imidic acid ester hydrochloride and glycine ester hydrochloride into the free esters and thus it would simplify the procedure and also avoid the loss of esters during their isolation. Therefore, after several experiments a general procedure was worked out which proved to be quite satisfactory and also gave very good yields which were comparable to those obtained by the direct condensation of

the esters according to the previously mentioned method I. Table IV gives an account of the imidazolones prepared by this method.

TABLE IV

Unsaturated imidazolones obtained by the condensation of aromatic aldehydes with a mixture of glycine ester and benzimidic acid ester hydrochlorides in the presence of sodium bicarbonate

Name	Structural formula	yield
2-Phenyl-4-benzylidene-5(4H)-imidazolone.		70.3%
2-Phenyl-4-(p-hydroxy-benzylidene)-5(4H)-imidazolone.		57.2%
2-Phenyl-4-anisylidene-5(4H)-imidazolone		79.3%
2-Phenyl-4-(3,4-dimethoxy-benzylidene)-5(4H)-imidazolone.		78.8%

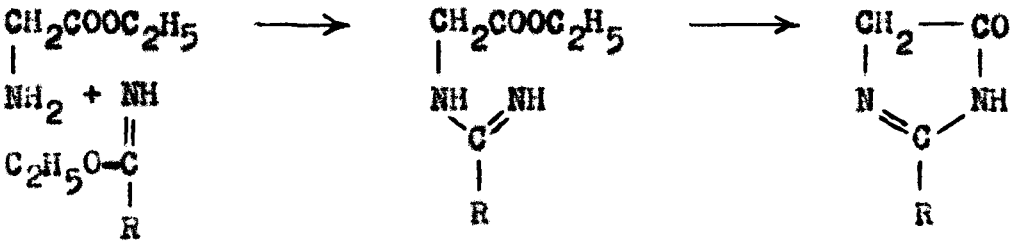
Procedure: The imidazolones were prepared by heating a mixture of an aldehyde, an imidic acid ester hydrochloride, and glycine ester hydrochloride taken in the ratio of 1:1.2: 1.5 with 10% excess of sodium bicarbonate in the presence of benzene for 1 hour in a water bath at 70-72°. The solid reactants were quickly mixed in a mortar and immediately transferred into a long-necked, round-bottomed flask. The carbonyl compound and the solvent were soon added and the mixture was heated at 70-72° with shaking in a pre-heated water bath till the imidazolone began to separate in 5-10 minutes. The flask was then kept vertically clamped in the water bath at that temperature, when a solid mass of yellow product was obtained. The product became slightly red coloured by the end of the reaction and the red colour became intense on removing the flask from the water bath due to the oxidation of unreacted 2-phenyl-5(4H)-imidazolone to glyoxaline red. The solid mass of imidazolone obtained was heated with alcohol, filtered hot and washed several times with alcohol and water.

A number of experiments were carried out with benzaldehyde to find out the optimum conditions for the reaction. When all the three reactants were used in equimolar amounts yield of the product was only 21.3% as compared to 70.3% yield obtained on taking benzaldehyde, benzimidic acid ester hydrochloride and glycine ester hydrochloride in the

ratio of 1:1.12:1.5. It was found that the operation such as the mixing of the solid reactants, transferring the mixture into the flask, adding the carbonyl compound and solvent and heating the mixture in a pre-heated water bath should be quickly done in order to obtain optimum yield. It was also noted that the mixture should be shaken constantly till the product starts separating, otherwise the yield is low.

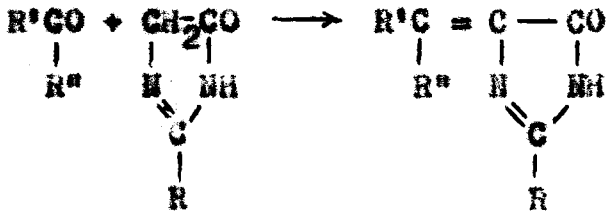
(c) Mechanism of the reaction

Since the imidic acid esters are known to react readily with ammonia and amines to form amidines it is assumed that this reaction is initiated by the condensation of the imidic acid ester with the amino group of the glycine ester to form the amidine which readily undergoes cyclisation to form the five membered ring structure of 2-substituted 5(4H)-imidazolone.

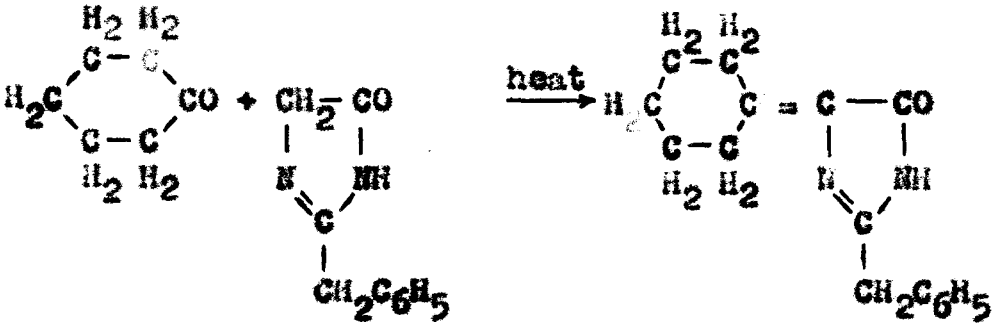


The 5(4H)-imidazolones possess a highly reactive methylene group which is doubly activated by the carbonyl group and the carbon-nitrogen unsaturated double bond flanking the

methylene group as in the case of azlactone. The methylene group in the imidazolone is so highly reactive that it undergoes condensation with carbonyl compounds readily even at room temperature without a catalyst since the basic character of the reactants may catalyse the reaction.

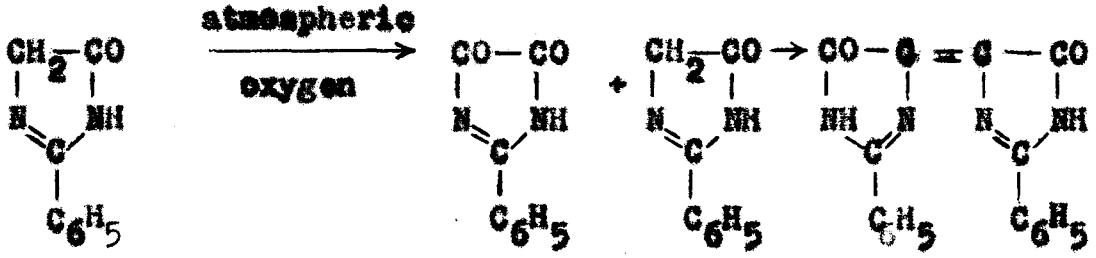


This sequence of the reactions is confirmed by the fact that in the earlier method of synthesis Finger (314,315) and Kjaer (316) have used presynthesised 2-substituted 5(4H)-imidazolone for the condensation with aldehydes. And Lehr and coworkers (317) synthesised 2-benzyl-4-cyclohexylidene-5(4H)-imidazolone by the condensation of cyclohexanone with preformed 2-benzyl-5(4H)-imidazolone.



Moreover, the condensation of carbon yl compound cannot be expected either with the methylene group of

glycine ester or with that of the intermediate open chain amidine and therefore it can be assumed that condensation of the carbonyl compound occurs only after the formation of the 2-substituted 5(4H)-imidazolone which possesses a very reactive methylene group. This is also confirmed by the very high reactivity of the unsubstituted 2-phenyl-5(4H)-imidazolone which undergoes spontaneous oxidation by the atmospheric oxygen forming glyoxaline red (314,316) which must be formed in an analogous manner as indigo.



(d) Scope and limitations

(1) Carbonyl compounds: Both aldehydes and ketones can be used in the synthesis of unsaturated imidazolones without the use of any catalyst. Aromatic as well as aliphatic aldehydes condense at room temperature to give very good yields of imidazolones. The aldehydes used in the condensation were benzaldehyde, p-hydroxybenzaldehyde, anisaldehyde, veratraldehyde, isobutyraldehyde and acetaldehyde. And the ketones used in the present work were acetone and methyl ethyl ketone. The yields were much

better in the case of 4-arylidene-5(4H)-imidazolones than in the case of the corresponding 4-alkylidene-5(4H)-imidazolones. It was also observed that substituted benzaldehydes gave slightly better yields than the unsubstituted benzaldehyde. The difference in the activity of the various aldehydes and ketones is illustrated in Table V with respect to the yields of the unsaturated imidazolones obtained.

All the condensation products of aromatic aldehydes were found to be quite stable. Only two 2,4-disubstituted 5(4H)-imidazolones namely 2-phenyl-4-isobutylidene-5(4H)-imidazolone and 2-phenyl-4-ethylidene-5(4H)-imidazolone were prepared by the condensation of aliphatic aldehydes. 2-Phenyl-4-isobutylidene-5(4H)-imidazolone was quite stable while 2-phenyl-4-ethylidene-5(4H)-imidazolone was found to be unstable. The ketones condensation products were comparatively unstable.

(ii) Imidic acid esters: In the present work only benzimidic acid ester, phenylacetimidic acid ester and acetimidic acid ester were used as typical examples of aromatic, arylaliphatic and aliphatic imidic acid esters. It was observed that benzimidic acid ester gave the condensation products in much higher yields than phenylacetimidic acid ester and acetimidic acid ester as indicated in Table VI.

TABLE V

Activity of various carbonyl compounds in the formation of unsaturated 2-Phenyl-imidazolones

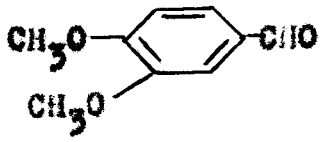
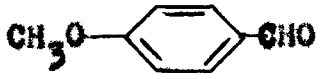
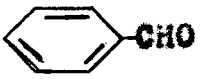
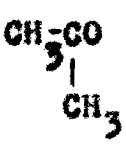
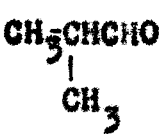
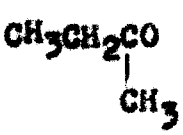
Carbonyl compounds		yield of imidazolone
Name	Structural formula	
Veratraldehyde		87.8%
p-Hydroxybenzaldehyde		85.6%
Anisaldehyde		85.2%
Benzaldehyde		76.3%
Acetone		64.2%
Isobutyraldehyde		55.6%
Methyl ethyl ketone		49.7%

TABLE VI

Effect of substituents in 2-position in the formation of unsaturated imidazolones

Carbonyl compound	Yield of unsaturated imidazolone		
	2-Phenyl	2-Benzyl	2-Methyl
Benzaldehyde	76.3%	46.4%	14.7%
Anisaldehyde	85.2%	48.7%	57.3%

(iii) Solvents: The condensation of aldehydes with the mixture of imidic acid ester and glycine ester proceeds quite smoothly even in the absence of a solvent at room temperature giving high yields but the product is obtained as a hard solid mass which is difficult to remove from the flask. Therefore, the use of solvent is advantageous. Benzene was found to be the most suitable solvent although toluene and xylene can also be used with equal advantage. However, in the condensation of benzaldehyde with phenylacetimidic ester no product was obtained when benzene was used as solvent but this reaction could be carried out satisfactorily using petroleum ether (b.p. 40-60°) as solvent.

For the condensation of methyl ethyl ketone benzene was used as solvent while in the case of acetone a large excess of it was taken to serve also the purpose of the solvent.

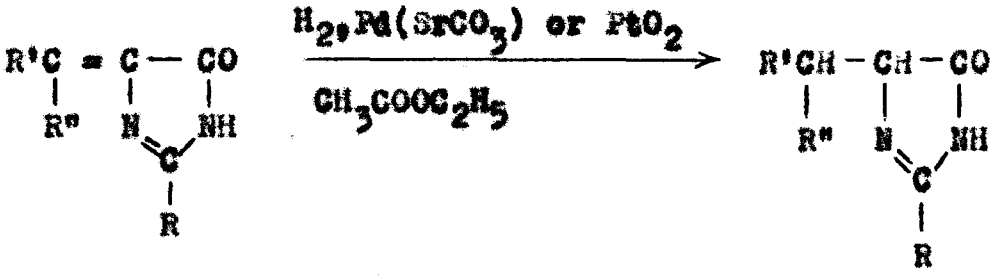
II: HYDROGENATION OF UNSATURATED 2,4-DISUBSTITUTED 5(4H)- IMIDAZOLONES

In 1927 Granacher and Gulbas (324) reduced unsaturated 2,4-disubstituted 5(4H)-imidazolones catalytically as well as with sodium amalgam in acetic acid and obtained 2,4-disubstituted 5-imidazolidones as a result of the saturation of both, the exocyclic and the ring double bonds. Williams and coworkers (325) obtained 85% yield of 2-phenyl-4-benzyl-5-imidazolidone by an improvement of Granacher's sodium amalgam reduction.

In 1953 Kjaer (306) selectively reduced the exocyclic double bond of 2-phenyl-4-benzylidene-5(4H)-imidazolone by hydrogenation using palladium oxide catalyst in the presence of alcohol and obtained 2-phenyl-4-benzyl-5(4H)-imidazolone, melting at 165-167° (rapid heating) but he did not report the yield. He has also not presented any chemical evidence in support of the reduction of the exocyclic double bond as against the ring double bond. When Kjaer's hydrogenation was repeated in connection with the present work only 30% yield of 2-phenyl-4-benzyl-5(4H)-imidazolone, melting at 167-168° (rapid heating), was obtained. The product was also found to be unstable in alcohol. The only other saturated 2,4-disubstituted 5(4H)-imidazolone prepared by reduction is 2-(2-hydroxyphenyl)-4-benzyl-

5(4H)-imidazolone (326). The yield was not reported in this case also.

For a successful synthesis of amino acids through imidazolones reduction of the exocyclic double bond of the unsaturated imidazolones in high yields is a crucial step. The reduction studies were carried out using a number of reducing agents. Obviously, reduction with a mixture of hydroiodic acid and red phosphorous, which has been very successfully used in the reduction and simultaneous hydrolysis of azlactones (137,138) into amino acids, drew the first attention. A mixture of hydroiodic acid and red phosphorous was used in the presence of glacial acetic acid as well as acetic anhydride for the reduction and hydrolysis of the imidazolones to amino acids but the attempts met with failures. Therefore, catalytic reduction was studied using platinum oxide, palladium on charcoal, palladium on barium sulphate and palladium on strontium carbonate in the presence of ethyl alcohol, acetic acid and ethyl acetate as solvents. After a number of experimentsit was found that platinum oxide and palladium on strontium carbonate in ethyl acetate provided the best conditions for the reduction of the exocyclic double bond of unsaturated imidazolones. The procedures are given



(a) Reduction with palladium on strontium carbonate

Palladium on strontium carbonate catalyst was prepared by treating a suspension of 50 g. of strontium carbonate in water at 70° with a solution of 1 g. of palladium chloride in dilute hydrochloric acid.

The unsaturated imidazolones are, generally, only slightly soluble in ethyl acetate in cold. Therefore, hydrogenation was carried out on a suspension of the imidazolone in ethyl acetate at room temperature and under atmospheric pressure using semi-micro hydrogenation apparatus. As the hydrogenation proceeded the unsaturated imidazolone went into solution. The saturated imidazolones are also, generally, insoluble in ethyl acetate therefore the reduction product separated as the hydrogenation progressed. When the substance absorbed one molecular proportion of hydrogen the absorption of hydrogen was practically or completely ceased. The time required for the hydrogenation ranged from 35 minutes to 5 hours. After filteration the product in the filterate was isolated by evaporating away the ethyl

acetate under reduced pressure in cold. The product in the residue was separated from the catalyst by dissolving in an excess of benzene by gentle heating, filtering and evaporating away benzene from the filterate under reduced pressure in cold. Table VII gives an account of the saturated imidazolones prepared by this method along with the yields obtained.

(b) Reduction with platinum:

Platinum oxide catalyst was prepared according to the method of Adams. A suspension of the unsaturated imidazolone in ethyl acetate was hydrogenated with platinum oxide in a semi-micro hydrogenation apparatus at room temperature and under atmospheric pressure. Only 2-phenyl-4-benzylidene-5(4H)-imidazolone and 2-phenyl-4-(p-hydroxybenzylidene)-5(4H)-imidazolone were hydrogenated by this method. As the hydrogenation proceeded the yellow unsaturated imidazolone went into solution and the pale yellow saturated imidazolone almost completely separated. The absorption of hydrogen was practically ceased when the substance absorbed one molecular proportion of hydrogen. The time taken for the hydrogenation was 1.5-2.5 hours. After filteration, 2-phenyl-4-benzyl-5(4H)-imidazolone was isolated from the residue by dissolving in an excess of benzene by gentle heating and filtering into a filteration flask containing petroleum ether

TABLE VII

Saturated imidazolones prepared by hydrogenation using palladium on strontium carbonate catalyst

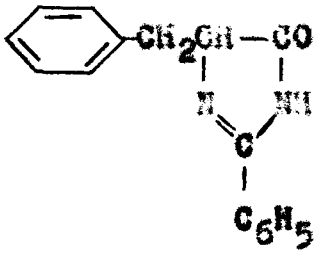
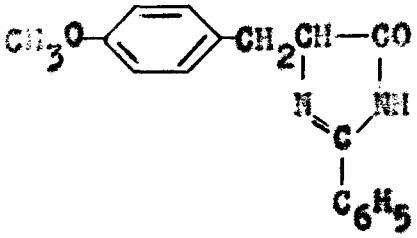
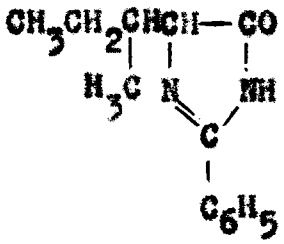
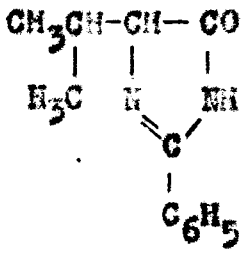
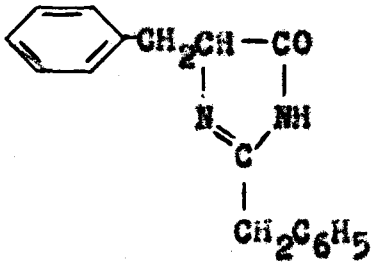
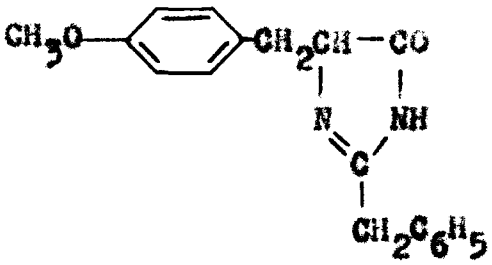
Name	Structural formula	yield
2-Phenyl-4-benzyl-5(4H)-imidazolone.		63.5%
2-Phenyl-4-anisyl-5(4H)-imidazolone		82.4%
2-Phenyl-4-sec-butyl-5(4H)-imidazolone		71.9%
2-Phenyl-4-isopropyl-5(4H)-imidazolone		74.9%

TABLE VII (continued)

Name	Structural formula	yield
2,4-Dibenzyl-5(4H)-imidazolone		59.5%
2-Benzyl-4-anisyl-5(4H)-imidazolone		64.6%

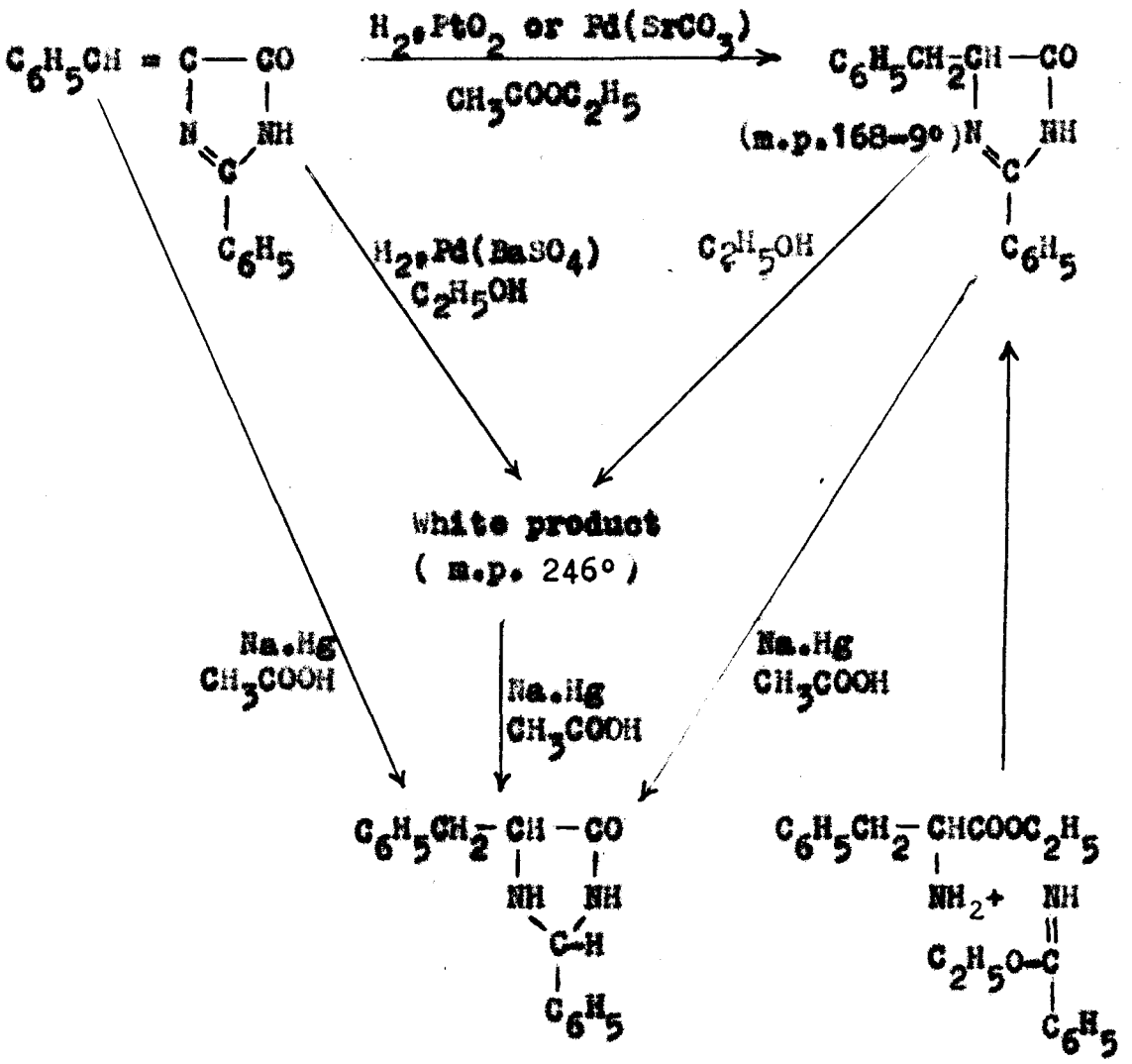
when the product precipitated immediately. The little product present in the filterate was isolated by evaporating away the ethyl acetate under reduced pressure in cold. The yield of 2-phenyl-4-benzyl-5(4H)-imidazolone was 84.1% while that of 2-phenyl-4-(p-hydroxybenzyl)-5(4H)-imidazolone was 86.8 per cent.

Initially the hydrogenation of 2-phenyl-4-benzylidene-5(4H)-imidazolone was studied in the presence of alcohol and acetic acid as solvents when a white crystalline product melting at 246° was obtained. This product was also obtained when 2-phenyl-4-benzyl-5(4H)-imidazolone, m.p. 168-169°

obtained by other methods, was subjected to recrystallisation from alcohol. However, 2-phenyl-4-benzylidene-5(4H)-imidazolone (324,325) 2-phenyl-4-benzyl-5(4H)-imidazolone and the white product melting at 246° gave the same 2-phenyl-4-benzyl-5-imidazolidone melting at 145° on reduction with sodium amalgam and acetic acid. Therefore, the white product, m.p. 246° may be considered to be a rearrangement product of 2-phenyl-4-benzyl-5(4H)-imidazolone melting at 168-169°. The structure of the product melting at 168-169° obtained on hydrogenation using ethyl acetate as solvent was confirmed by its unambiguous synthesis from phenylalanine ethyl ester and benzimidic acid ethyl ester. These reactions are outlined on the following page.

Platinum oxide and palladium on strontium carbonate were found to be very effective catalysts giving 60-87% yields when ethyl acetate was used as solvent. The hydrogenations were not successful when palladium oxide, palladium on carbon and palladium on barium sulphate were used in the case of 2-phenyl-4-benzylidene-5(4H)-imidazolone in the presence of ethyl acetate as solvent.

In general imidazolones with substituted benzylidene groups at 4-position took more time for hydrogenation than the corresponding imidazolones with unsubstituted benzylidene group. Again, imidazolones with alkylidene groups at



4-position were hydrogenated more readily than those with benzylidene groups in 4-position. Unsaturated imidazolones with benzyl group at 2-position were more readily hydrogenated than those with phenyl group at this position. It may also be mentioned in this connection that hydrogenation of 2-phenyl-4-(p-hydroxybenzylidene)-5(4H)-imidazolone was not reproduceable.

(e) **Properties:**

2-Phenyl-4-benzyl-5(4H)-imidazolones are pale yellow compounds while the other saturated imidazolones are white in colour. Compared to the corresponding unsaturated 2,4-disubstituted 5(4H)-imidazolones the saturated imidazolones are less stable. However, the saturated imidazolones with phenyl group at 2-position can be kept at room temperature for a few weeks without decomposition. The saturated imidazolones containing benzyl radical in 2-position start decomposing within one or two days. In general these compounds are soluble in common organic solvents, acids and alkalies. The solutions of saturated imidazolones in organic solvent especially in hydroxylic solvents are unstable. Therefore the isolations were carried out in cold under reduced pressure, and recrystallisations were done by dissolving in excess of benzene by gentle heating and filtering the solution into petroleum ether, when the saturated imidazolones were immediately precipitated.

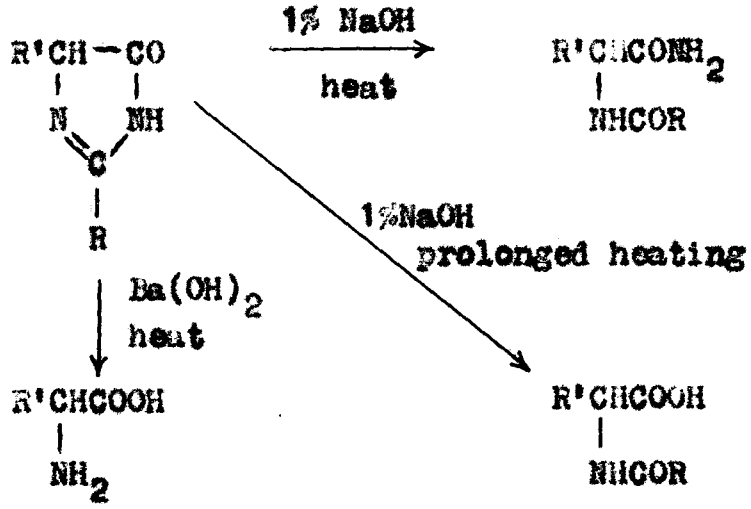
III: HYDROLYSIS OF SATURATED 2,4-DISUBSTITUTED 5(4H)-IMIDAZOLONES

In the azlactone synthesis of amino acids (137,138) reduction and hydrolysis of the azlactones into the corresponding amino acids or acylamino acids are carried out simultaneously, using hydroiodic acid and red phosphoreus in the presence of either acetic anhydride or acetic acid. However, in the case of imidazolones reduction and simultaneous hydrolysis was not successful. But the catalytic reduction of unsaturated imidazolones to the saturated imidazolones could be carried out conveniently. Therefore, for the synthesis of amino acids and their derivatives hydrolysis of the saturated imidazolones was an essential step.

In 1948 Cornforth and Huang (305) hydrolysed 2-phenyl-4-methyl-5(4H)-imidazolone with phosphoric acid as well as 20% sodium hydroxide solution and detected the presence of alanine in the reaction mixture by the ninhydrin test. This is the only instance of the hydrolysis of a saturated 2,4-disubstituted 5(4H)-imidazolone reported in the literature.

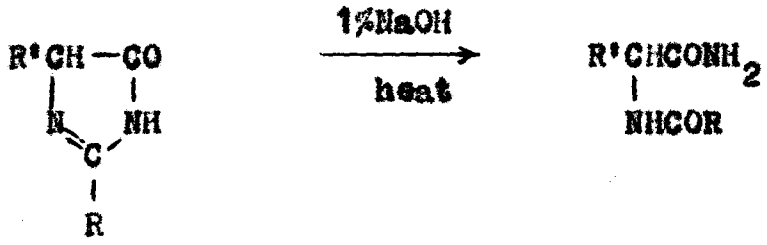
The above conditions of hydrolysis are far from satisfactory for a preparative method and therefore systematic studies for the hydrolysis of the imidazolone ring were undertaken so that the imidazolones could be hydrolysed to

the corresponding acyl amino acid amides, acylamino acids and amino acids under suitable conditions when satisfactory results were obtained.



(a) Acylamino acid amides

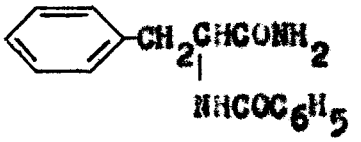
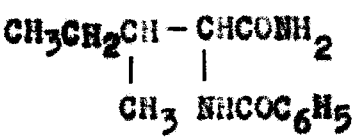
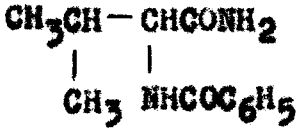
There was facile hydrolysis of the saturated 2,4-di-substituted 5(4H)-imidazolones when heated with 1% sodium hydroxide solution. The saturated imidazolone readily dissolved when heated with 1% sodium hydroxide solution to form a pale yellow solution and within a few minutes of refluxing there was separation of acylamino acid amide.



The Table VIII gives an account of the acylamino acid amides prepared by this method.

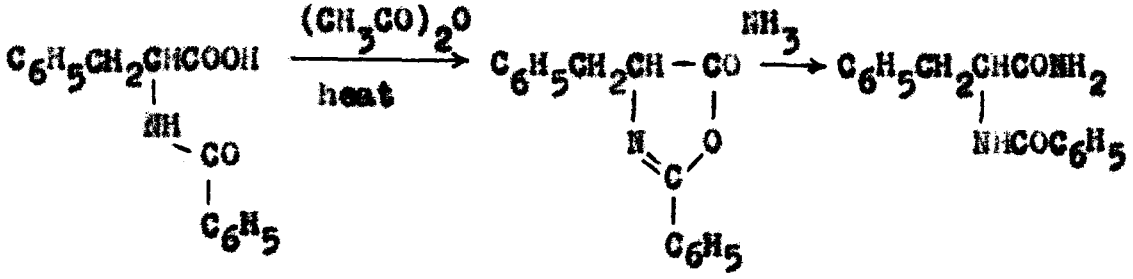
TABLE VIII

Acylamino acid amides

Name	Structural formula	yield
Benzoylphenylalanine amide		26.6%
Benzoylisoleucine amide		68.3%
Benzoylvaline amide		46.8%
Phenylacetylphenyl-alanine amide		29.3%

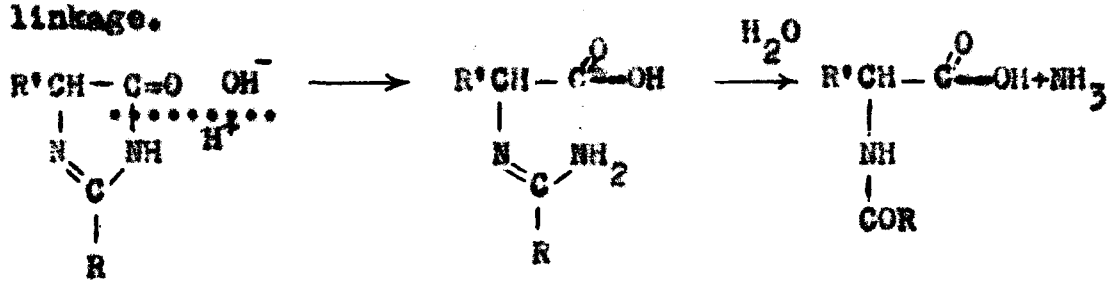
The yields of the acylamino acid amides were not very high because the heating with alkali also hydrolyses the amides to acylamino acids. It is interesting to point out that benzoylphenylalanine amide and phenylacetylphenylalanine amide are hydrolysed to the corresponding acylamino acids more readily than benzoylvaline amide and benzoylisoleucine amide. Benzoylphenylalanine amide, a typical member of this class was identified by its hydrolysis to benzoylphenyl-alanine and also through its synthesis by the azlactone

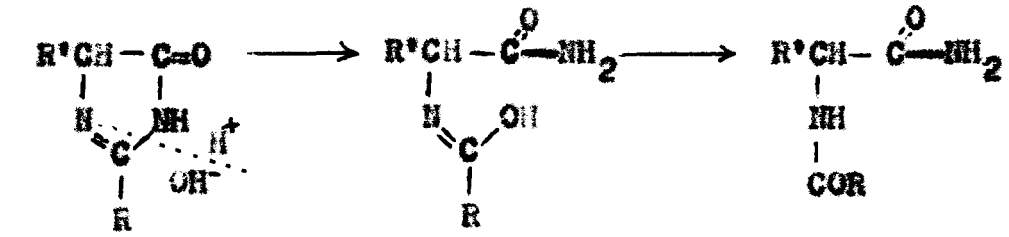
method (334).



In addition to the azlactone method there is only one more method for the synthesis of acylamino acid amides namely through acylamino acid chlorides and therefore imidazolones offer a new method for the synthesis of acylamino acid amides.

In the normal course, alkaline hydrolysis of imidazolones would be expected to lead to the cleavage of the 1-5 linkage with the formation of the carboxylic acid and ammonia by an initial attack of the hydroxy ion on the carbonyl carbon in 5-position but the formation of acylamino acid amides indicates the course of hydrolysis involving the attack of hydroxy ion on the amidine carbon in 2-position of the imidazolone ring with the consequent cleavage of the 1-2 linkage.



OR 

(b) Acylamino acids

The saturated 2,4-disubstituted 5(4H)-imidazolones were converted into acylamino acids by refluxing with 1% sodium hydroxide solution for 1.5–4 hours. On heating under reflux the saturated imidazolone readily dissolved in the sodium hydroxide solution to form a pale yellow solution and the acylamino acid amide separated within a few minutes of refluxing. On further refluxing the amide dissolved with evolution of ammonia to form acylamino acid. The unhydrolysed imidazolone was precipitated by saturating the solution with carbon dioxide and removed by filteration. The aqueous solution was further purified by extraction with ethyl acetate and acidified with hydrochloric acid when the acylamino acid was precipitated.

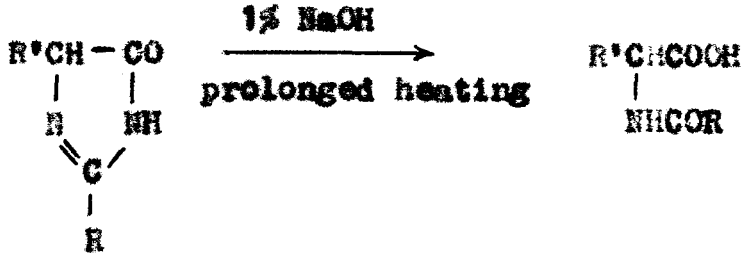
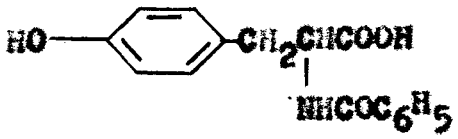
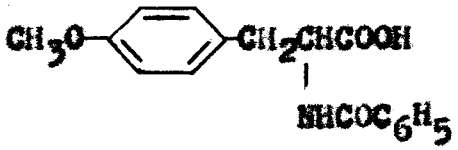
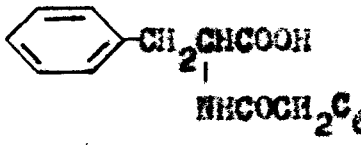
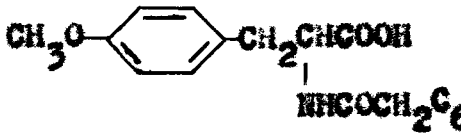


Table IX gives an account of the acylamino acids thus prepared.

TABLE IX

Acylamino acids

Name	Structural formula	yield
Benzoylphenyl-alanine.		68.5%
N-Benzoyltyrosine		19.4%
Benzoyl-O-methyl-tyrosine.		47.8%
Phenylacetyl-phenylalanine.		74.9%
Phenylacetyl-O-methyltyrosine.		69.8%

It was observed in the case of 2-phenyl-4-isopropyl-5(4H)-imidazolone and 2-phenyl-4-sec-butyl-5(4H)-imidazolone that the acylamino acid amides obtained were quite stable therefore they could not be hydrolysed with 1% sodium hydroxide solution. In the case of 2-phenyl-4-(p-hydroxy-benzyl)-5(4H)-imidazolone no amide separated during hydrolysis

which may be due to the solubility of the product in sodium hydroxide solution because of the phenolic nature of the compound.

The availability of acylamino acids in the imidazolone synthesis similar to the azlactone synthesis is of considerable advantage since acylamino acids are largely used for the resolution of amino acids.

(c) Amino acids

Amino acids were prepared by refluxing saturated 2,4-disubstituted 5(4H)-imidazolones with about 5 molecular proportions of a 40% barium hydroxide solution for 7.5 hours. On refluxing with barium hydroxide the imidazolone was dissolved and hydrolysed with evolution of ammonia. After diluting the reaction mixture with water the barium was precipitated with excess of dilute sulphuric acid and removed. The solution was concentrated to a certain extent under reduced pressure from a water bath at 50-55°, and the benzoic acid was removed by extraction with ether. The solution was again concentrated to a small volume and its pH was adjusted with liquor ammonia, when the amino acid separated. After cooling in the refrigerator it was filtered and washed with water and alcohol.

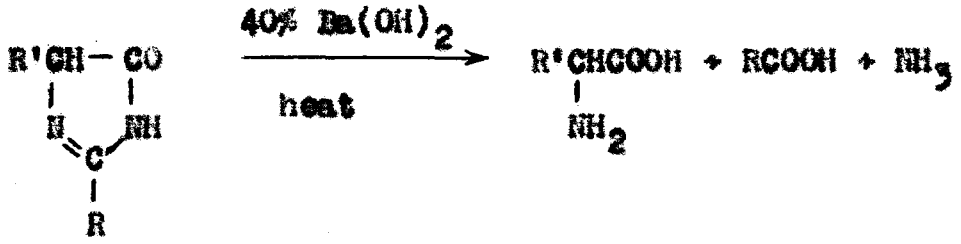
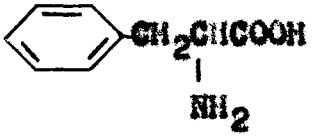
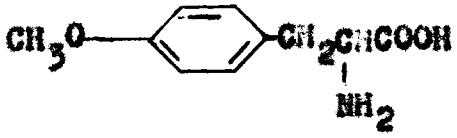
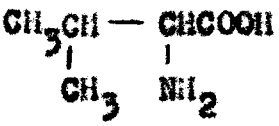


Table X gives an account of the amino acids prepared by this method.

TABLE X

Amino acids

Name	Structural formula	yield
Phenylalanine		67.9%
O-Methyltyrosine.		58.9%
Valine.		31.9%

In the case of phenylalanine 43.6% over-all yield was obtained which compares favourably with the 41% yield of phenylalanine by the azlactone method (137).

In the preparation of O-methyltyrosine the corresponding azlactone cannot be subjected to reduction and simultaneous hydrolysis with hydroiodic acid and red phosphorous since it leads to demethylation. So the azlactone is first converted into acylamino cinnamic acid and then reduced with sodium amalgam to the acylamino acid which is then hydrolysed to O-methyltyrosine (328). The yield of O-methyltyrosine prepared by this method is not reported. However, O-methyltyrosine was obtained in 41.3% over-all yield by the imidazolone method.

In the case of valine the yield was only 32 per cent.

It would be of interest to point out that so far no systematic degradation of 2,4-disubstituted 5(4H)-imidazolones was carried out to prove their structure. Therefore the present work provides conclusive evidence of the structure of imidazolones through the stepwise degradations and identification of the products.

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EXPERIMENTAL

EXPERIMENTAL*

I: SYNTHESES OF STARTING MATERIALS

1. Glycine ethyl ester hydrochloride

Glycine ethyl ester hydrochloride was prepared essentially according to the method developed by Curtius and Goebel (335) and improved by others (336,337).

A mixture of 75 g. (1 mole) of glycine and 750 ml. absolute ethyl alcohol was taken in a 2-l round-bottomed flask, fitted with a white rubber cork carrying an inlet tube and a calcium chloride tube. Hundred grams (2.7 mole) of hydrogen chloride gas, dried by bubbling through concentrated sulphuric acid and passing over phosphorus pentoxide, was absorbed in the mixture at room temperature. Then the mixture was heated under reflux using a coiled condenser fitted with a white rubber cork and carrying a calcium chloride tube. The glycine was completely dissolved within about 0.5 hour but it was refluxed for 2 hours more. When the solution attained room temperature it was seeded with a few crystals of glycine ethyl ester hydrochloride. The crystallisation started immediately and the solution was

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* Melting points are uncorrected. Analyses were performed by M/S. Alfred Bernhardt, Mikroanalytisches Laboratorium, im Max-Planck-Institut, fur Kohlenforschung, Mulheim (Ruhr) W.Germany.

full of crystals within a short while. The flask was allowed to stand in a refrigerator overnight. The crystals were filtered, washed twice with 100-ml. portions of ice-cold absolute ethyl alcohol and dried in an oven at about 80° for 1 hour. The perfectly white needle like crystalls of glycine ethyl ester hydrochloride melting at 144-145° weighed 111.7 g. (30.1%). Harvel (105) and Chambers and Carpenter (337) reported melting points 142-143° and 145-148° respectively.

The mother liquor and the washings were concentrated to about 100 ml. and seeded with a little glycine ethyl ester hydrochloride and kept in the refrigerator. On the next day the crystals separated were filtered, washed with ice-cold absolute ethyl alcohol and dried when 16.7 g.(11.9%) of white crystals of m.p. 138-140° were obtained. The total yield of glycine ethyl ester hydrochloride was 128.4 g. (92%).

2. <u>Glycine ethyl ester</u>

Glycine ethyl ester hydrochloride was converted into glycine ethyl ester essentially according to the method of Fischer (338,339).

Twenty five grams (0.18 mole) of glycine ethyl ester hydrochloride was taken in a 500-ml. conical flask and dissolved in 30 ml. of distilled water. To this 100 ml. of

ether was added, cooled in an ice bath and neutralised by adding 20 ml. of an ice-cold sodium hydroxide solution (40%). It was treated with potassium carbonate by keeping the flask in ice bath till the aqueous layer was saturated. The contents of the flask was transferred into a separating funnel, shaken well and the ether layer was collected in a 500-ml. conical flask. The aqueous layer was further extracted twice with 50-ml. portions of ether. The combined ether extracts were treated with anhydrous potassium carbonate by keeping the flask in ice bath. It was placed in the refrigerator for 6 hours, filtered through a fluted filter paper by decantation and the residue was washed thrice with ether dried over sodium metal. When the ether was evaporated away under reduced pressure by shaking the flask in cold water 16.1 g. (87.2%) of colourless glycine ethyl ester was obtained. It was used for the condensation without further purification.

3. Imidic acid ester hydrochlorides

Imidic acid ester hydrochlorides were prepared according to the method originated by Pinner (340) and improved by others (317, 341-347).

(a) Benzimidic acid ethyl ester hydrochloride

A mixture of 51 ml. (0.5 mole) of benzonitrile and 31.5 ml. (0.54 mole) of absolute ethyl alcohol was taken in a 500-ml.

filteration flask fitted with a cork carrying an inlet tube. A calcium chloride tube was attached to the side tube of the flask. The mixture was cooled in a freezing mixture and 22 g. (0.60 mole) of hydrogen chloride gas, dried by bubbling through concentrated sulphuric acid and passing over phosphorous pentoxide was absorbed in it. After the reaction was over the flask was closed with a rubber stopper and left in the freezing mixture. After 5 hours benzimidic acid ethyl ester hydrochloride started separating as white crystals. The flask was allowed to stand at room temperature for about 3 days, the hard white crystalline mass of benzimidic acid ethyl ester hydrochloride formed was carefully broken into pieces, transferred into a dry mortar, quickly powdered and taken in a 500-ml. dry conical flask. To this 150 ml. of ether dried over sodium metal was added, the flask was closed with a rubber stopper and kept at room temperature overnight. It was filtered on a Buchner funnel, washed twice with 50-ml. portions of dry ether. The product was dried in a vaccum dessicator over potassium hydroxide pellets and phosphorous pentoxide. The yield of white benzimidic acid ethyl ester hydrochloride melting at 117° with decomposition was 88 g. (94.9%). Pinner (340) and MacKenzie and coworkers (344) reported melting points 118-120° and 128-129° respectively.

(b) Phenylacetimidic acid ethyl ester hydrochloride

A mixture of 113 ml. (0.98 mole) of benzylcyanide, 58 ml. (0.99 mole) of absolute ethyl alcohol and 230 ml. of ether dried over sodium metal was taken in a 1-l. round-bottomed pyrex flask fitted with a cork carrying an inlet tube and a calcium chloride tube. The flask with its contents was cooled in a freezing mixture and 40 g. (1.1 mole) of hydrogen chloride gas, dried by bubbling through concentrated sulphuric acid and passing over phosphorous pentoxide was absorbed in it. The flask was closed with a white rubber cork, tied and placed in the refrigerator. The solution became pale yellow after some time. On the next day it was seeded with a little phenylacetimidic acid ethyl ester hydrochloride and shaken, when crystallisation started. After keeping for two days more in the refrigerator it was filtered. As the product was slightly yellow in colour, it was transferred into a conical flask and treated with dry ether. Within a few hours it became perfectly white, when it was filtered and dried in a vaccum dessicator over phosphorous pentoxide. The product weighed 120 g. and melted at 94-95°. On keeping the mother liquor in the refrigerator for three days a further crop of 25 g. was obtained. A third crop of 15 g. of crystals was also obtained after a few days. So the total yield of phenylacetimidic acid ethyl ester hydrochloride was 160 g.

(81.8%).

(c) Acetimidic acid ethyl ester hydrochloride

In a filteration flask fitted with a cork carrying an inlet tube, a mixture of 31.9 ml. (0.61 mole) of acetonitrile and 35.75 ml. (0.61 mole) of absolute ethyl alcohol was taken. A calcium chloride tube was attached to the side tube of the flask. The flask with its contents was cooled in a freezing mixture and 24.25 g. (0.66 mole) of dry hydrogen chloride gas (dried by bubbling through concentrated sulphuric acid and passing over phosphorous pentoxide) was absorbed in it. The flask was closed with a white rubber cork and allowed to stand at room temperature. Within a few hours the entire reaction mixture was almost completely solidified into a white crystalline mass. After two days the crystalline solid mass was broken treated with about 50 ml. of ether dried over sodium metal and kept overnight. The product was filtered off, washed three times with dry ether and dried in a vaccum dessicator over potassium hydroxide pellets and pohosphorous pentoxide. The yield was 68 g. (90.5%).

4. Imidic acid esters

Imidic acid ester hydrochlorides were converted into imidic acid esters essentially according to the method employed by Lehr and collaborators (317).

(a) Benzimidic acid ethyl ester

Twenty five grams (0.13 mole) of benzimidic acid ethyl ester hydrochloride was dissolved in 30 ml. of distilled water. To this 60 ml. of ether was added, cooled in ice and neutralised by slowly adding 16 ml. of ice-cold sodium hydroxide solution (40%). It was transferred into a separating funnel, shaken well and the ether layer was collected in a 250-ml. conical flask. To the aqueous layer 30 ml. of ether was added and the aqueous layer was saturated with potassium carbonate by keeping the flask in the ice bath. After shaking the mixture in the separating funnel the ether layer was collected along with the first ether extract. The aqueous layer was once again extracted with 30 ml. of ether. The combined ether solution of the benzimidic acid ethyl ester was treated with anhydrous potassium carbonate by keeping the flask in the ice bath. It was allowed to stand in the refrigerator for 6 hours, filtered and the residue was washed thrice with dry ether. The etherial extract was evaporated under reduced pressure when 19.3 g. (96.1%) of practically colourless benzimidic acid ethyl ester was obtained.

(b) Phenylacetimidic acid ethyl ester

Phenylacetimidic acid ethyl ester hydrochloride (25 g., 0.125 mole) was dissolved in 23 ml. of distilled water,

60 ml. of ether was added to it, cooled in an ice bath and neutralised with 14 ml. of ice-cold sodium hydroxide solution (40%) by slowly adding while the flask was shaken in an ice bath. The contents of the flask were transferred into a separating funnel, shaken well and the ether layer was collected in a conical flask. To the aqueous layer 30 ml. of ether was added and it was saturated with potassium carbonate by keeping the flask in the ice bath. It was transferred into the separating funnel, shaken and the ether extract was collected. The aqueous layer was once again extracted with 30 ml. of ether. The combined ether extracts were treated with anhydrous potassium carbonate by keeping the flask in the ice bath. It was then allowed to stand in the refrigerator for 6 hours, filtered and the ether was completely evaporated away under reduced pressure when quantitative yield of perfectly colourless and clear phenylacetimidic acid ethyl ester was obtained.

(c) <u>Acetimidic acid ethyl ester</u>

Acetimidic acid ethyl ester hydrochloride (3.3 g., 0.027 mole) was dissolved in minimum amount of distilled water, cooled in an ice bath and neutralized with 3 ml. of ice-cold sodium hydroxide solution (40%). After adding 20 ml. of ether the aqueous layer was saturated with potassium carbonate.

The contents of the flask were transferred into a separating funnel, shaken well and the ether layer was collected. The aqueous layer was extracted twice more with 20-ml. portions of ether. The combined ether extracts were treated with anhydrous potassium carbonate by keeping the flask in the ice bath. After keeping in the refrigerator for four hours it was filtered together with the ether solution of the glycine ethyl ester obtained from 5 g. of its hydrochloride, the ether was evaporated away under reduced pressure and the mixture of esters thus obtained was used for condensation with aldehydes.

II: SYNTHESES OF UNSATURATED 2,4-DISUBSTITUTED 5(4H)-IMIDAZOLONES

1. 2-Phenyl-4-benzylidene-5(4H)-imidazolone

Method I: Benzimidic acid ethyl ester, 8 ml. (0.054 mole), glycine ethyl ester, 5.6 ml. (0.056 mole), pure dry benzene, 15 ml. and benzaldehyde, 4.8 ml. (0.048 mole) were quickly mixed in a 150-ml. conical flask, closed and kept at room temperature (25°) with occasional shaking. The solution gradually became yellow and then changed to red. After about 30 minutes yellow imidazolone began to separate in plenty. The flask was allowed to stand for 20 hours, when a solid mass of yellow product with red tinge was obtained. When the flask was opened the product became red coloured due to the oxidation of unreacted 2-phenyl-5(4H)-imidazolone to glyoxaline red by atmospheric oxygen. The solid mass was broken by means of a glass rod, heated with 75 ml. of ethyl alcohol in a water bath and filtered hot on a glass sintered funnel. The filterate was red coloured. The product was thoroughly washed four times with 40-ml. portions of ethyl alcohol, and dried in an oven at 80° for 1 hour. The yellow coloured 2-phenyl-4-benzylidene-5(4H)-imidazolone weighed 9 g. (76.3%) and melted at 272-273°.

Method II: Ten grams (0.054 mole) of benzimidic acid ethyl ester hydrochloride, 10 g. (0.072 mole) of glycine ethyl ester

hydrochloride and 11.66 g. (0.14 mole) of sodium bicarbonate were quickly mixed well in a dry mortar and the mixture was immediately transferred into a 250-ml. dry round-bottomed flask with a long neck. To this 20 ml. of pure dry benzene and then 4.8 ml. (0.048 mole) of benzaldehyde were at once added and the flask was soon transferred into a water bath already heated to 72°. The flask was shaken constantly and the temperature of the water bath was maintained at 70-72°. There was vigorous effervescence of carbon dioxide due to reaction of the ester hydrochlorides with sodium bicarbonate and yellow imidazolone began to separate in plenty within 10 minutes. Now the shaking was stopped and the flask was kept vertically clamped in the water bath at that temperature for 50 minutes, when an yellow solid mass of imidazolone was obtained with slight red tinge. When the flask was taken out from the water bath and allowed to cool the red colour became more intense. The solid mass was broken in the flask by means of a glass rod. To this 100 ml. of ethyl alcohol was added, the flask was heated in water bath and the product was filtered hot on a glass sintered funnel. The filterate was deep red coloured. The product was first washed thoroughly 5 times with 40-ml. portions of ethyl alcohol, then 5 times with 40-ml. portions of distilled water and finally once with

40 ml. of ethyl alcohol. It was dried in the oven at 80° for 1 hour. The yield of yellow 2-phenyl-4-benzylidene-5(4H)-imidazolone melting at 272-273° was 8.20 g. (70.3%). Recrystallisation: 2-Phenyl-4-benzylidene-5(4H)-imidazolone (0.5 g.) was heated to boil with 45 ml. of amylacetate, when it was completely dissolved. It was filtered and the filterate was allowed to stand at room temperature, when yellow crystals began to separate immediately. On the next day, the crystals separated were filtered on a Hirsch funnel and washed thrice with 5-ml. portions of ethyl alcohol. The product was dried in the oven at 80° for one hour. The yellow crystals weighed 0.427 g. (85.4%) and melted at 273-274°. The mixed melting point of this substance with an authentic sample was also 273-274°. Erlenmeyer (299), Ekeley and Ronzio (310) and Cornforth and Huang (305) reported melting points 270°, 284°, and 272-273° respectively. The infra red spectra of this substance and the authentic sample were identical.

Anal. Found: C, 77.77; H, 4.84; N, 11.21

Calc. for $C_{16}H_{12}ON_2$: C, 77.40; H, 4.87; N, 11.28

2. 2-Phenyl-4-(p-hydroxybenzylidene)-5(4H)-imidazolone

Method I: Eight millilitres (0.054 mole) of benzimidic acid ethyl ester, 5.6 ml. (0.056 mole) of glycine ethyl ester and 15 ml. of pure dry benzene were quickly mixed in a 150-ml.

conical flask. To this mixture 5.6 g. (0.046 mole) of p-hydroxybenzaldehyde was immediately added, closed and shaken well. The aldehyde readily dissolved to form a red orange solution. The flask was allowed to stand at room temperature (23°) with occasional shaking. Yellow imidazolone began to separate after about 20 minutes and on further shaking plenty of it separated. Then the flask was kept without shaking and the reaction mixture was completely solidified into a yellow mass soon. After keeping the flask at room temperature for a total of 22 hours, the flask was opened and the deep yellow solid mass was broken by means of a glass rod. Now it became red brown tinged. It was heated with 75 ml. of glacial acetic acid in a boiling water bath, cooled under the water tap and filtered on a glass sintered funnel. The filterate was red coloured. The product was washed thrice with 40-ml. portions of ice-cold alcohol and dried in the oven at 80° for 1 hour. The deep yellow 2-phenyl-4-(p-hydroxybenzylidene)-5(4H)-imidazolone weighed 10.29 g. (85.6%) and melted at 288-289°.

Method II: Five grams (0.027 mole) of benzimidic acid ethyl ester hydrochloride, 5 g. (0.036 mole) of glycine ethyl ester hydrochloride, 5.83 g. (0.07 mole) of sodium bicarbonate and 2.8 g. (0.023 mole) of p-hydroxybenzaldehyde were quickly mixed well in a dry mortar and the mixture was immediately

transferred into a 250-ml. dry round-bottomed flask with a long neck. To this 10 ml. of pure dry benzene was added soon and the flask was at once transferred into a water-bath already heated to 72°. The flask was shaken constantly and the temperature of the water bath was maintained at 70-72°. There was very vigorous effervescence and frothing and the mixture turned yellow, orange and finally settled down to a red orange solid within 5 minutes. Then the flask was kept vertically clamped in the water bath at that temperature for 55 minutes without shaking. The red orange solid product was treated with 35 ml. of glacial acetic acid, when the product became yellow. It was heated in a boiling water bath, cooled under the water tap and filtered on glass sintered funnel. The filterate was deep red coloured. The product was washed thrice with 20-ml. portions of ice-cold alcohol then thrice with 20-ml. portions of distilled water and finally once with 20 ml. of ice-cold alcohol. It was dried in the oven at 80° for 1 hour. The yield of orange yellow 2-phenyl-4-(p-hydroxybenzylidene)-5(4H)-imidazolone melting at 287-288° was 3.46 g. (57.2%).

Recrystallisation: 2-Phenyl-4-(p-hydroxybenzylidene)-5(4H)-imidazolone (6 g.) was dissolved in ethyl alcohol (240 ml.) by heating to boil. It was filtered through a fluted filter paper using a hot water funnel and the red orange filterate

was allowed to stand at room temperature overnight. The crystals separated were filtered on a Buchner funnel, washed twice with 15-ml. portions of alcohol and dried in the oven. The yield of the orange yellow crystals melting at 291-292° was 4 g. (66.7%).

Anal. Found: C, 72.97; H, 4.80; N, 10.48

$C_{16}H_{12}O_2N_2$ requires: C, 72.71; H, 4.58; N, 10.60

3. 2-Phenyl-4-anisylidene-5(4H)-imidazolone

Method I: Benzimidic acid ethyl ester, 4 ml.(0.027 mole), glycine ethyl ester, 2.8 ml. (0.028 mole), pure dry benzene, 7.5 ml. and anisaldehyde, 2.9 ml. (0.024 mole) were quickly mixed in a 100-ml. conical flask and kept closed at room temperature (23°) with occasional shaking. The solution gradually became orange yellow and within about 30 minutes yellow imidazolone began to separate in plenty. Then the flask was left without shaking and within few hours it was completely solidified into an yellow mass. After a total of 22 hours of keeping the flask at room temperature the yellow mass was broken by means of a glass rod, heated with 40 ml. of ethyl alcohol in a water bath and filtered hot on a glass sintered funnel. The filterate was red coloured. The product was thoroughly washed four times with 20-ml. portions of ethyl alcohol and dried in the oven at 80° for one hour. The bright

yellow crystals of 2-phenyl-4-anisylidene-5(4H)-imidazolone weighed 5.67 g. (85.2%) and melted at 288-289°.

Method II: Benzimidic acid ethyl ester hydrochloride, 10 g. (0.054 mole), glycine ethyl ester hydrochloride, 10 g. (0.072 mole) and sodium bicarbonate, 11.66 g. (0.14 mole) were quickly mixed well in a dry mortar and the mixture was immediately transferred into a dry 250-ml. round-bottomed flask with a long neck. To this first 20 ml. of pure dry benzene and then 5.8 ml. (0.048 mole) of anisaldehyde were soon added and the flask was at once transferred into a water bath already heated to 72°. The flask was shaken constantly and the temperature of the water bath was maintained at 70-72°. The two ester hydrochlorides reacted vigorously with sodium bicarbonate, and the yellow imidazolone began to separate within 7 minutes. Now the shaking was stopped and the flask was kept vertically clamped in the water bath at that temperature for 53 minutes. The reaction mixture was completely solidified into a yellow mass within 15 minutes from the beginning of the reaction. When the flask was removed from the water bath the yellow solid mass became slightly red coloured. It was broken by means of a glass rod, heated with 100 ml. of ethyl alcohol in a water bath and filtered hot on a glass sintered funnel. The filterate was red coloured. It was washed thoroughly 5 times with

40-ml. portions of ethyl alcohol, then five times with 40-ml. portions of distilled water and finally once with 40 ml. of ethyl alcohol. The product was dried in the oven at 80° for 1 hour. The weight of the bright yellow 2-phenyl-4-anisylidene-5(4H)-imidazolone melting at 288-289° was 10.56 g. (79.3%).

Recrystallisation: 2-Phenyl-4-anisylidene-5(4H)-imidazolone, 0.5 g. was heated to boil with 95 ml. of amylacetate, when it completely dissolved to form a yellow solution. It was filtered and allowed to stand at room temperature overnight, when yellow spongy needles of the imidazolone separated. The crystals were filtered and washed thrice with 5-ml. portions of alcohol and dried in the oven at 80° for 1 hour. The bright yellow spongy needles weighed 0.413 g. (82.6%). It melted at 289-290°. The melting point reported by Cornforth and Huang (305) is also 289-290°.

Anal. Found: C, 73.15; H, 5.08; N, 10.17

Calc. for $C_{17}H_{14}O_2N_2$: C, 73.36; H, 5.07; N, 10.07

4. 2-Phenyl-4-(3,4-dimethoxybenzylidene)-5(4H)-imidazolone

Method I: Benzimidic acid ethyl ester (4 ml., 0.027 mole), glycine ethyl ester (2.8 ml., 0.028 mole) and pure dry benzene (7.5 ml.) were quickly mixed in a 100-ml. conical flask. To this powdered veratraldehyde (3.9 g., 0.023 mole) was added,

the flask was closed and shaken well. The aldehyde readily dissolved to form a pale yellow solution. The flask was allowed to stand at room temperature with occasional shaking, when the solution gradually became red orange. After about 1 hour yellow crystals of imidazolone began to separate. On further shaking plenty of crystals separated and the mixture was almost solidified within a few minutes. The flask was allowed to stand for 20 hours more at the room temperature without shaking. The yellow solid mass was broken, heated with 40 ml. of ethanol and filtered hot on a glass sintered funnel. The filterate was pale red coloured. The product was washed 4 times with 40-ml. portions of ethanol and dried in the oven at 80° for 1 hour. The bright yellow 2-phenyl-4-(3,4-dimethoxybenzylidene)-5(4H)-imidazolone weighed 6.35 g. (87.8%) and melted at 258-259°.

Method II: Five grams (0.027 mole) of benzimidic acid ethyl ester hydrochloride, 5 g. (0.036 mole) of glycine ethyl ester hydrochloride, 5.83 g. (0.07 mole) of sodium bicarbonate and 5.9 g. (0.023 mole) of veratraldehyde were quickly mixed well in a dry mortar and the mixture was at once transferred into a 250-ml. dry round-bottomed flask with a long neck. Immediately 10 ml. of pure dry benzene was added to it and the flask was soon heated with constant shaking in a water

bath already heated to 70°. The temperature of the water bath was maintained at 70-72°. There was vigorous effervescence of carbon dioxide, the solid ester hydrochlorides were converted into liquid esters and yellow imidazolone began to separate within 7 minutes. The shaking was stopped and the flask was kept vertically clamped in the water bath at 70-72° for 53 minutes. An yellow solid mass of product was obtained which developed slight red tinge towards the end of the reaction. The solid mass was broken, heated with 75 ml. of ethyl alcohol and filtered hot on a glass sintered funnel. The filterate was red coloured. The product was washed five times with 40-ml. portions of alcohol, then five times with 40-ml. portions of distilled water and finally once with 40 ml. of alcohol and dried in the oven at 80° for 1 hour. The yield of bright yellow 2-phenyl-4-(3,4-dimethoxybenzylidene)-5(4H)-imidazolone melting at 258-259° was 5.7 g. (78.8%).

Recrystallisation: 2-Phenyl-4-(3,4-dimethoxybenzylidene-5(4H)-imidazolone (0.75 g.) was dissolved in 25 ml. of ethyl benzoate by heating to boil & the orange yellow solution was filtered and kept at room temperature overnight. The crystals separated were filtered off and washed thrice with 10 ml. portions of ether. After drying the weight of the orange yellow crystals melting at 258-259° was 0.67 g. (89.3%). Ekeley and Elliott (311) reported melting point 259-260°.

Anal. Found: C, 69.82; H, 5.46; N, 9.00

Calc. for $C_{13}H_{16}O_3N_2$: C, 70.11; H, 5.23; N, 9.09

5. 2-Phenyl-4-isobutylidene-5(4H)-imidazolone:

Benzimidic acid ethyl ester, 4 ml. (0.027 mole), glycine ethyl ester, 2.8 ml. (0.028 mole), pure dry benzene, 7.5 ml. and isobutyraldehyde, 2.1 ml. (0.023 mole) were quickly mixed in a 100-ml. dry conical flask, closed and kept at room temperature (17°) with occasional shaking. The solution gradually became red coloured. The shaking was stopped as soon as crystals of the imidazolone began to separate. The flask was allowed to stand for 18 hours, when a large quantity of white crystals formed. The crystals were filtered on a glass sintered funnel. The filterate was red coloured. The product was washed five times with 5-ml. portions of ice-cold alcohol and dried in the oven at 80° for 1 hour. The weight of the almost white 2-phenyl-4-isobutylidene-5(4H)-imidazolone was 2.75 g. (55.6%). It melted at 174-176°.

Recrystallisation: Well powdered 2-phenyl-4-isobutylidene-5(4H)-imidazolone (0.75 g.) was dissolved in 20 ml. of benzene by heating in a water bath at about 73° with shaking for 2 minutes. The solution was filtered and the pale brown filterate was allowed to stand at room temperature overnight. The crystals separated were filtered on a Hirsch funnel, washed thrice with 2-ml. portions of ether, and dried. The

almost white crystals weighed 0.575 g. (76.7%) and melted at 180.5-181°. On a further crystallisation from the same solvent absolutely white crystals melting at 181.5-182° were obtained. Kjaer (306) reported m.p. 182°.

Anal. Found: C, 73.32; H, 6.53; N, 12.79

Calc. for $C_{13}H_{14}ON_2$: C, 72.87; H, 6.59; N, 13.08

6. 2-Phenyl-4-sec-butylidene-5(4H)-imidazolone:

Twelve millilitres (0.081 mole) of benzimidic acid ethyl ester, 8.25 ml. (0.082 mole) of glycine ethyl ester, 30 ml. of dry benzene and 9 ml. (0.10 mole) of pure methyl ethyl ketone were mixed in a 100-ml. standard-joint flask. The flask was fitted with a condenser carrying a calcium chloride tube and heated in an already heated water bath. The mixture soon became red coloured. Crystals of the imidazolone began to separate after about 2 hours. It was refluxed for 5 hours totally. The flask was closed before the reaction mixture was completely cooled down and placed in the refrigerator overnight, when a lot of crystals separated. It was filtered on a glass sintered funnel. The filterate was deep red. The product was thoroughly washed twice with 30-ml. portions of ice-cold alcohol and then five times with 30-ml. portions of ether. After drying, the cream coloured 2-phenyl-4-sec-butylidene-5(4H)-imidazolone weighed 8.69 g (49.7%). It

melted at 173-174° with decomposition.

Recrystallisation: 2-Phenyl-4-sec-butylidene-5(4H)-imidazolone (0.75 g.) was heated with dioxane (10 ml.) in a water bath at about 75° for 1 minute, when it completely dissolved to form a pale brown solution. It was filtered and kept at room temperature. After 5 hours, the crystals separated were filtered off, and washed thrice with 2-ml. portions of ether and dried. The white crystals weighed 0.225 g. (30%) and melted at 173.5-174.5° with decomposition. A further recrystallisation from the same solvent afforded perfectly white crystals melting at 174.5-175.5° with decomposition.

Anal. Found: C, 72.84; H, 6.44; N, 13.12

$C_{13}H_{14}ON_2$ requires: C, 72.87; H, 6.59; N, 13.08

7. 2-Phenyl-4-isopropylidene-5(4H)-imidazolone:

Benzimidic acid ethyl ester, 8 ml. (0.054 mole), glycine ethyl ester, 5.5 ml. (0.054 mole) dry acetone, 25 ml. were quickly mixed in a 100-ml. standard-joint flask and immediately heated in an already heated water bath after fitting a reflux condenser carrying a calcium chloride tube. The mixture gradually became brown and after about two hours white crystals of the imidazolone began to separate. It was refluxed for 7 hours totally and by that time a lot of imidazolone separated. Before the reaction mixture was completely

cooled down, the flask was closed and placed in the refrigerator overnight. It was filtered on a glass sintered funnel. The filterate was red brown. The crystals were thoroughly washed twice with 10-ml. portions of ice-cold alcohol and then twice with 10-ml. portions of ether and dried. The weight of the almost white 2-phenyl-4-isopropylidene-5(4H)-imidazolone melting at 191-192° with decomposition was 6.54 g. From the mother liquor on concentration under reduced pressure 0.425 g. of a little more coloured product was obtained. The total yield of 2-phenyl-4-isopropylidene-5(4H)-imidazolone was 6.97 g. (64.2%).

Recrystallisation: Well powdered 2-phenyl-4-isopropylidene-5(4H)-imidazolone, 0.75 g. was dissolved in dioxane, 10 ml. by heating in a water bath at about 73° for 1.5 minutes with shaking. The pale yellow solution was obtained was filtered and allowed to stand at room temperature. The crystals separated were filtered off after 2.5 hours, washed thrice with 3-ml. portions of ether and dried. The white crystals weighed 0.35 g. (46.7%) and melted at 192-192.5° with decomposition. Lehr and coworkers (317) reported m.p. 200-201° (corr.)

Anal. Found: C, 72.40; H, 6.08; N, 13.60

Calc. for $C_{12}H_{12}ON_2$: C, 71.93; H, 6.04; N, 13.99

8. 2-Benzyl-4-benzylidene-5(4H)-imidazolone:

A mixture of 16.5 g. (0.10 mole) of phenylacetimidic acid ethyl ester, 10.5 g. (0.10 mole) of glycine ethyl ester, and 11 ml. (0.11 mole) of benzaldehyde and 60 ml. of petroleum ether (b.p. 40-60°) was taken in a 500-ml three-necked flask fitted with a mechanical stirrer, reflux condenser and a dropping funnel. The mixture was refluxed for 3.5 hours with stirring. The imidazolone began to separate within 15 minutes and the solution became coloured. After about 2 hours of refluxung 10 ml. of petroleum ether was added in order to replace the loss. The product was treated with benzene when the refluxing was over and kept overnight. It was filtered, washed with benzene and dried. The pale yellow 2-benzyl-4-benzylidene-5(4H)-imidazolone weighed 11 g. It melted at 175-176°. A further crop of 1.3 g. of product was obtained from the mother liquor on concentration. So the total yield was 12.3 g. (46.4%).

Recrystallisation: 2-Benzyl-4-benzylidene-5(4H)-imidazolone (4.75 g.) was dissolved in 100 ml. of distilled benzene by heating in a water bath and the solution was filtered through a fluted filter paper using a hot water funnel. The flask was washed by heating 5 ml. of benzene in it and filtered into the main bulk. The pale brown filterate was allowed to stand at room temperature. The crystals separated were

filtered on a glass sintered funnel after two days. The crystals were washed twice with 12-ml. portions of distilled benzene and dried. The pale yellow crystals weighed 3.6 g. (75.8%) and melted at 177-178°. Finger and Zeh (315) reported m.p. 177.5°

Anal. Found: C, 77.84; H, 5.50; N, 10.57

Calc. for $C_{17}H_{14}ON_2$: C, 77.84; H, 5.38; N, 10.68

9. 2-Benzyl-4-anisylidene-5(4H)-imidazolone:

Phenylacetimidic acid ethyl ester and glycine ethyl ester obtained, respectively, from 5 g. (0.025 mole) and 4.5 g. (0.032 mole) of the corresponding ester hydrochlorides were taken in a reaction tube, 2.3 ml. (0.019 mole) of anisaldehyde and 6 ml. of pure dry benzene were added, the tube was sealed and shaken well, when the solution became yellowish brown. It was kept at room temperature (20°). After about 4 hours yellow imidazolone began to separate. The reaction tube was kept at room temperature totally for about 24 hours. The imidazolone separated was filtered off, washed with benzene and dried. The yellow product melting at 184-185° with decomposition weighed 2.7 g. (48.7%).

Recrystallisation: 2-Benzyl-4-anisylidene-5(4H)-imidazolone (0.5 g.) was dissolved in 30 ml. of distilled benzene by heating in a water bath. The solution was filtered through

a fluted filter paper. The yellow filterate was allowed to stand at room temperature overnight. The crystals separated were filtered off, washed thrice with 3-ml. portions of distilled benzene and dried in the oven. The yellow crystals weighed 0.395 g. (79) and melted at 186-187° with decomposition

Anal. Found: C, 74.23; H, 5.75; N, 9.65

$C_{18}H_{16}O_2N_2$ requires: C, 73.95; H, 5.52; N, 9.58

10. 2-Methyl-4-benzylidene-5(4H)-imidazolone

Method I: Glycine ethyl ester and acetimidic acid ethyl ester obtained, respectively, from 5 g. (0.036 mole) and 3.3 g. (0.027 mole) of the corresponding ester hydrochlorides were mixed in a dry test tube. To this 5 ml. of dry benzene and 2.2 ml. (0.022 mole) of benzaldehyde were added, the test tube was tightly corked, shaken well and allowed to stand at room temperature. The colour of the reaction mixture turned red brown and after about 1 hour yellow crystals began to separate. On the next day the crystals were filtered off, washed with ether and dried. The yield of pale yellow 2-methyl-4-benzylidene-5(4H)-imidazolone was 0.5 g. (14.7%). It melted at 169-172° with decomposition.

Method II: Five grams (0.036 mole) of glycine ethyl ester hydrochloride, 3.3 g. (0.027 mole) of acetimidic acid ethyl ester hydrochloride and 5.3 g. (0.063 mole) of sodium

bicarbonate were mixed well in a mortar and the mixture was taken in a 100-ml. dry round-bottomed flask. To this 2.3 ml. (0.023 mole) of benzaldehyde and 5 ml. of dry xylene were added and heated in a water bath at about 70°. In the beginning there was vigorous effervescence and the hydrochlorides of the esters were converted into liquid esters. No imidazolone separated even though it was heated for 1 hour. In the beginning the flask was shaken. The solution became yellow coloured. On cooling pale yellow crystals of imidazolone separated. The product was filtered off and washed with distilled water and ether. The yield was 1 g. (20.1%).

Recrystallisation: On recrystallisation from benzene pale yellow crystals melting at 177.5-178.5° with decomposition was obtained. Kjaer (306) reported m.p. 169-172°.

Anal. Found: C, 71.01; H, 5.41; N, 14.99

Calc. for $C_{11}H_{10}ON_2$: C, 70.92; H, 5.41; N, 15.05

11. 2-Methyl-4-anisylidene-5(4H)-imidazolone:

A mixture of glycine ethyl ester and acetimidic acid ethyl ester obtained respectively from 5 g. (0.036 mole) and 3.3 g. (0.027 mole) of the corresponding ester hydrochlorides was taken in a dry test tube. To this 2.5 ml. (0.021 mole) of anisaldehyde and 5 ml. of dry benzene were added, the test tube was tightly corked, shaken well and allowed to stand at room temperature. The solution gradually became red brown

and after about 30 minutes yellow crystals began to separate. Now on shaking plenty of imidazolone separated. After two days the crystals were filtered off. The yellow 2-methyl-4-anisylidene-5(4H)-imidazolone melting at 198-199° with decomposition weighed 2.2 g. (57.3%).

Recrystallisation: 2-Methyl-4-anisylidene-5(4H)-imidazolone (0.5 g.) was recrystallised from distilled benzene (70 ml.). The yield of yellow needle shaped crystals melting at 201-202° with decomposition was 0.363 g. (73%).

Anal. Found:	C, 66.74; H, 5.66; N, 12.84
$C_{12}H_{12}O_2N_2$ requires:	C, 66.65; H, 5.59; N, 12.96

III: HYDROGENATION OF UNSATURATED 2,4-DISUBSTITUTED 5(4H)-IMIDAZOLONES

Catalyst: Platinum oxide catalyst was prepared according to the method of Adams (348). Palladium on strontium carbonate catalyst was prepared as follows essentially according to the directions given in the pamphlet supplied along with the Tower's hydrogenation apparatus. A boiling solution of 106 g. of hydrated strontium chloride in 1l. of distilled water was treated with a hot solution of 43 g. of anhydrous sodium carbonate in 150 ml. of distilled water, when strontium carbonate precipitated. The mixture was boiled for about 0.5 hour in order to make the precipitate granular. When the precipitate settled down it was filtered and washed several times with distilled water by decantation. The strontium carbonate was dried in an oven at about 110° and powdered well. A suspension of 50 g. of strontium carbonate in 400 ml. of distilled water at 70° was treated with a hot solution of palladium chloride (prepared by dissolving 1 g. of palladium chloride in a mixture of 2.5 ml. of pure hydrochloric acid and 6.5 ml. of distilled water by heating on a steam bath for 1 hour with occasional shaking) with constant stirring. The stirring was continued for 10 minutes while the temperature of the mixture was being maintained at 70°. When the brown coloured catalyst settled down it was filtered on a glass

sintered funnel and washed several times with distilled water by decantation till the washings were practically free from chloride ions. It was dried in a vaccum dessicator over solid potassium hydroxide and powdered well. The catalyst weighed 46.9 g. It was transferred into a glass-stoppered conical flask and kept in a dessicator over solid potassium hydroxide.

1. 2-Phenyl-4-benzyl-5(4H)-imidazolone

Method 1: Five grams (0.020 mole) of crude 2-phenyl-4-benzylidene-5(4H)-imidazolone (powdered), 50 mg. of platinum oxide catalyst and 50 ml. of ethyl acetate were taken and hydrogenated in a Tower's semi-micro hydrogenation apparatus under a pressure of 15 mm. higher than atmospheric pressure and at room temperature (26°). When the hydrogenation was started most of the yellow 2-phenyl-4-benzylidene-5(4H)-imidazolone remained undissolved. It gradually dissolved and the pale yellow saturated imidazolone separated as the hydrogenation proceeded. The absorption of hydrogen was rapid although the rate slowly decreased with time. The absorption of hydrogen practically ceased after 2.25 hours by that time one molecular proportion of hydrogen was absorbed by the substance. The flask was shaken for 15 minutes more. The contents of the flask were filtered using a glass sintered funnel. (The filterate was used to transfer the solid material

completely from the flask). The filterate was removed from the filteration flask and evaporated to dryness under reduced pressure by shaking the flask in cold water. The residue obtained was treated with 10 ml. of ether & filtered on a Hirsch funnel. It was washed twice with 5-ml. portions of ether and dried. The yield of pale yellow 2-phenyl-4-benzyl-5(4H)-imidazolone was 0. 485 g. It melted at 165-166.5° to a clear pale yellow liquid on rapid heating (the rise of temperature was about 13° per minute at about the m.p.).

After removing the filterate from the filteration flask the residue containing the catalyst and most of the hydrogenation product was dried by suction. It weighed 4.12 g. The powdered residue was taken in a 250-ml. conical flask and heated with 140 ml. of distilled benzene in a water bath at about 74° for 3 minutes with shaking, when the product dissolved. The solution was filtered with suction through a glass sintered funnel into 150 ml. petroleum ether (b.p. 60-80°). Plenty of crystals of imidazolone separated in the filteration flask immediately. The conical flask was washed by heating 10 ml. of benzene in it and filtered into the main bulk. It was allowed to stand at room temperature for 5 hours. The crystals were collected on a glass sintered funnel, washed twice with 20-ml. portions of petroleum ether (b.p. 60-80°) and dried by suction. The weight of the pale

yellow 2-phenyl-4-benzyl-5(4H)-imidazolone was 3.76 g. (74.6%). It melted at 168-169° to a very clear pale yellow liquid on rapid heating (the rise of temperature was 13° per minute at about the melting point). The total yield was 4.24 g. (84.1%).

Method II: Crude 2-phenyl-4-benzylidene-5(4H)-imidazolone (5 g., 0.020 mole), palladium on strontium carbonate catalyst (5 g.) and ethyl acetate (50 ml) were taken and hydrogenated at room temperature (24°) and under a pressure of 20 mm. higher than atmospheric pressure using Tower's semi-micro hydrogenation apparatus. Most of the yellow 2-phenyl-4-benzylidene-5(4H)-imidazolone remained undissolved when the hydrogenation was started. But as the hydrogenation proceeded it gradually dissolved and the pale yellow saturated imidazolone separated. The rate of absorption of hydrogen was almost uniform till the substance absorbed one molecular proportion of hydrogen within about four hours. Then there was practically no more absorption of hydrogen. The flask was shaken for 1.5 hours more, disconnected, cooled in the refrigerator for 1 hour and filtered. (The filterate was used to transfer the solid materials completely from the flask). After drying by suction the residue containing the catalyst and most of the product weighed 9.1 g.

The above residue was well powdered and 4.55 g. of it was heated with 70 ml. of distilled benzene in a water bath at about 75° for about 2 minutes with shaking. The solution of the product obtained was filtered through a fluted filter paper by decantation. The pale yellow crystals of the imidazolone began to separate immediately in the filterate. To the conical flask containing the catalyst 5 ml. of benzene was added, heated and filtered into the main bulk. After keeping the flask in the ice chest of a refrigerator for 2.5 hours it was kept outside till the benzene crystallised remelted. The product was filtered and washed thrice with 10 ml. portions of dry ether. The yield of pale yellow 2-phenyl-4-benzyl-5(4H)-imidazolone melting at 164° to a very clear liquid (on rapid heating) was 1.6 g. (63.5%).

Recrystallisation: 2-Phenyl-4-benzyl-5(4H)-imidazolone (0.25 g.) isolated from the residue containing the platinum catalyst and the substance was dissolved in 10 ml. of distilled benzene by heating in a water bath at about 72° for 3 minutes. The solution was filtered into 10 ml. of petroleum ether (b.p. 60-80°). The crystals of the imidazolone began to separate immediately. After 5 hours, the crystals separated were filtered on a Hirsch funnel, washed thrice with 3 ml. portions of distilled ether and dried by suction. The pale yellow crystals of 2-phenyl-4-benzyl-5(4H)-imidazolone melted

at 168-169° to a very clear pale yellow liquid on rapid heating (the rise of temperature was about 13° per minute at about the m.p.). The mixed melting point of this substance with 2-phenyl-4-benzyl-5(4H)-imidazolone obtained by condensing phenylalanine ethyl ester and benzimidic acid ethyl ester was also 168-169°. Kjaer (306) reported m.p. 165-167°
The infra red spectra of these two samples were identical.

Anal. Found: C, 76.83; H, 5.48; N, 11.68

Calc. for $C_{16}H_{14}ON_2$: C, 76.78; H, 5.64; N, 11.19

2. 2-Phenyl-4-(p-hydroxybenzyl)-5(4H)-imidazolone

Four grams (0.015 mole) of recrystallised 2-phenyl-4-(p-hydroxybenzylidene)-5(4H)-imidazolone, 50 mg. of platinum oxide catalyst and 75 ml. of ethyl acetate were taken and hydrogenated in a Tower's semi-micro hydrogenation apparatus under a pressure of about 20 mm. higher than atmospheric pressure and at room temperature (34°). When the hydrogenation was started most of the 2-phenyl-4-(p-hydroxybenzylidene)-5(4H)-imidazolone was undissolved but as the hydrogenation proceeded the orange yellow unsaturated imidazolone gradually went into solution to give a pale yellow saturated imidazolone which precipitated from the solution. The hydrogenation was over within 1.5 hours. The product was filtered on a Buchner funnel and washed thrice with 25 ml. portions of distilled

ether and dried. The pale yellow 2-phenyl-4-(p-hydroxybenzyl)-5(4H)-imidazolone containing the catalyst weighed 3.55 g.(86.8%)

3. 2-Phenyl-4-anisyl-5(4H)-imidazolone

Two grams (0.0072 mole) of well powdered, crude 2-phenyl-4-anisylidene-5(4H)-imidazolone was hydrogenated using 6 g. of palladium on strontium carbonate catalyst in the presence of 100 ml. of ethyl acetate in a Tower's sem-micro hydrogenation apparatus at room temperature and under a pressure of 15 mm. higher than atmospheric pressure. Most of the yellow 2-phenyl-4-anisylidene-5(4H)-imidazolone remained undissolved at the beginning of the hydrogenation. It gradually dissolved as the hydrogenation proceeded and a practically colourless solution of the saturated imidazolone was obtained after about 5 hours. However, the shaking of the flask was continued for 15 minutes. The flask was disconnected and the solution was filtered through a glass sintered funnel. The residue was washed twice with 7.5 ml. portions of ethyl acetate. The filterate and the washings were immediately evaporated to dryness under reduced pressure by shaking the flask in cold water. The residue was treated with 30 ml. of distilled ether and filtered on a glass sintered funnel. The product was washed twice with 10-ml. portions of ether and dried. The weight of the slightly pale yellow 2-phenyl-4-anisyl-5(4H)-imidazolone was 1.66 g.(82.4%). It melted to a clear

and pale yellow liquid at 144-149° on rapid heating.

Recrystallisation: 2-Phenyl-4-anisyl-5(4H)-imidazolone (0.4 g.) was dissolved in 50 ml. of benzene by heating in a water bath at about 67° for 2 minutes, the solution was transferred into centrifuge tubes, cooled and centrifuged in order to remove the collidal catalyst present in it. It was filtered using a fluted gravimetric filter paper and the filterate was concentrated to about 15 ml. under diminished pressure by shaking the flask in cold water. The crystals separated were redissolved by heating with shaking for 1.5 minutes at 72°. The pale yellow solution was filtered into 15 ml. of petroleum ether (b.p. 60-80°) through a fluted gravimetric filter paper. It was allowed to stand at room temperature for 5 hours and the crystals separated were filtered on a Hirsch funnel. The crystals were washed four times with 3-ml. portions of distilled ether and dried. The pale yellow crystals weighed 0.2 g. (50%) and melted at 155-159° to a very clear pale yellow liquid on rapid heating. On a further crystallisation from the same solvent the melting point was raised to 160-161°.

Anal. Found:	C, 72.72; H, 5.44; N, 9.67
$C_{17}H_{16}O_2N_2$ requires:	C, 72.84; H, 5.75; N, 9.99

4. 2-Phenyl-4-Sec-butyl-5(4H)-imidazolone

In a Tower's semi-micro hydrogenation apparatus crude 2-phenyl-4-Sec-butylidene-5(4H)-imidazolone (5 g., 0.023 mole) was hydrogenated at room temperature (18°) and under a pressure of 15 mm. higher than atmospheric pressure using palladium on strontium carbonate catalyst (5 g.) in the presence of ethyl acetate (75 ml.). In the beginning a good part of the unsaturated imidazolone remained undissolved. It gradually dissolved and the reduction product separated as the hydrogenation proceeded. The absorption of hydrogen was rapid in the beginning but the rate gradually decreased with time and after about four hours by that time one molecular proportion of hydrogen was absorbed, there was a sudden and constant fall in the rate of absorption of hydrogen. However, the shaking of the flask was continued for 1 hour. The flask was disconnected and the contents were filtered using a glass sintered funnel. About 15 ml. of ethyl acetate was used to transfer the solid materials completely from the flask. The pale brown filterate was transferred into a flask and then the residue was dried by suction. The residue weighed 8.02 g. and it contained the catalyst and a part of the hydrogenation product.

The pale brown filterate was immediately evaporated to

dryness under reduced pressure by shaking the flask in cold water. The white residue containing a little pale brown material was treated with 15 ml. of ether and filtered on a glass sintered funnel. The product was washed twice with 7.5 ml. portions of ether and dried. The white 2-phenyl-4-sec-butyl-5(4H)-imidazolone weighed 0.92 g. It melted at 140.5-142.5° to a pale brown liquid.

The residue containing the catalyst and the hydrogenation product was powdered, taken in a conical flask and heated with 65 ml. of distilled benzene in a water bath at 72° for 3 minutes with shaking, when the product was dissolved. The solution was filtered through a glass sintered funnel and the residue was washed with 10 ml. of hot benzene. A white residue containing a little pale brown substance was obtained when the filterate was evaporated to dryness under reduced pressure by shaking the flask in a cold water bath. It was treated with 20 ml. of ether, filtered on a glass sintered funnel, washed twice with 7.5 ml. portions of ether and dried. The perfectly white product weighed 2.71 g. and melted at 141-143° to a pale brown liquid. The total yield of 2-phenyl-4-sec-b tyl-5(4H)-imidazolone was 3.63 g. (71.9%).

Recrystallisation: 2-Phenyl-4-sec-b tyl-5(4H)-imidazolone (0.2 g.) was dissolved in benzene (4 ml.) by heating with shaking for 3 minutes in a water bath at 73° and the solution

was filtered into 4 ml. of petroleum ether (b.p. 60-80°). It was allowed to stand at room temperature for 3.5 hours and the crystals separated were filtered on a Hirsch funnel. It was washed thrice with 2-ml. portions of ether and dried. The crystals were absolutely white and melted at 142-144° to a pale brown liquid.

Anal. Found: C, 72.73; H, 7.59; N, 12.80

$C_{13}H_{16}ON_2$ requires: C, 72.19; H, 7.46; N, 12.95

5. <u>2-Phenyl-4-isopropyl-5(4H)-imidazolone</u>

Five grams (0.025 mole) of crude 2-phenyl-4-isopropylidene-5(4H)-imidazolone was hydrogenated using 5 g. of palladium on strontium carbonate catalyst in the presence of 75 ml. of ethyl acetate in a Tower's semi-micro hydrogenation apparatus, under a pressure of 15 mm. higher than atmospheric pressure and at room temperature (28°). When the hydrogenation was started a good part of the 2-phenyl-4-isopropylidene-5(4H)-imidazolone remained undissolved. As the hydrogenation proceeded it gradually dissolved and the saturated imidazolone separated. In the beginning the rate of absorption of hydrogen was very high but it gradually decreased, and there was a sudden and constant fall in the rate after about 3 hours by that time one molecular proportion of hydrogen was absorbed. To transfer the solid materials completely from the flask 10 ml.

of ethyl acetate was used. The slightly pale brown filterate was removed from the flask and the residue was dried by suction. This residue containing the catalyst and a part of the hydrogenation product weighed 7.69 g.

The filterate was evaporated to dryness under reduced pressure by shaking the flask in cold water. The white residue containing slight pale yellow substance was treated with 15 ml. of ether and filtered on a glass sintered funnel. It was washed twice with 5-ml. portions of ether and dried. The white product weighed 1.297 g. and melted at 158.5-161° to a red brown liquid.

The residue containing the catalyst and a part of the hydrogenation product was well powdered, taken in a conical flask, 50 ml. of benzene was added and heated with shaking for 3 minutes in a water bath at 75°, when the product was dissolved. The solution was filtered through a glass sintered funnel by decantation. The catalyst was washed by heating with 10 ml. of benzene and filtered into the main bulk. The pale yellow filterate was evaporated to dryness under reduced pressure by shaking the flask in cold water. The white residue containing a slight pale brown substance was treated with 30 ml. of ether. It was transferred to a glass sintered funnel, washed twice with 10-ml. portions of ether and dried. The product was white and it weighed 2.48 g. It melted at

158-161° to a red brown liquid. The total yield was 3.78 g. (74.9%).

Recrystallisation: 2-Phenyl-4-isopropyl-5(4H)-imidazolone (0.3 g.) was dissolved in distilled benzene (20 ml.) by heating in a water bath at 70° for 1 minute, the solution was transferred into centrifuge tubes, cooled and centrifuged in order to remove the colloidal catalyst present in it. It was filtered through a gravimetric filter paper, concentrated to about 6 ml. under reduced pressure by shaking the flask in cold water. The crystals separated were redissolved by heating in a water bath at about 70° for 1 minute with shaking and filtered through a gravimetric filter paper into 4 ml. of petroleum ether (b.p. 60-80°). It was allowed to stand at room temperature. After about 3.5 hours the crystals separated were filtered with suction, washed thrice with 1.5-ml. portions of distilled ether and dried. The white crystals weighed 0.16 g. (53.3%) and melted at 161-163° to a red brown liquid.

Anal. Found:	C, 71.55; H, 6.95; N, 14.01
$C_{12}H_{14}ON_2$ requires:	C, 71.26; H, 6.98; N, 13.85

6. 2,4-Dibenzyl-5(4H)-imidazolone

Three grams (0.011 mole) of recrystallised 2-benzyl-4-benzylidene-5(4H)-imidazolone, 5 g. of palladium on strontium

carbonate catalyst and 50 ml. of distilled ethyl acetate were taken and hydrogenated in a Tower's semi-micro hydrogenation apparatus at room temperature and under a pressure of 20 mm. higher than atmospheric pressure. The hydrogenation was over in 35 minutes. The solid unsaturated imidazolone was converted into soluble saturated imidazolone. The solution was soon filtered through a glass sintered funnel and the residue was washed with 15 ml. of ethyl acetate. The filterate and washings were immediately evaporated to dryness under reduced pressure by keeping the flask in cold water. The crystalline residue was treated with 20 ml. of ether dried over sodium metal. It was filtered on a glass sintered funnel, washed twice with 10-ml. portions of dry ether and dried. The yield of almost white product melting at 114-124° was 1.8 g. (59.5%).

7. 2-Benzyl-4-anisyl-5(4H)-imidazolone

Recrystallised 2-benzyl-4-anisylidene-5(4H)-imidazolone (1 g., 0.0034 mole), palladium on strontium carbonate catalyst (2 g.) and ethyl acetate (25 ml.) were taken and hydrogenated under a pressure of about 20 mm. higher than atmospheric pressure and at room temperature (35°) using a Tower's semi-micro hydrogenation apparatus. The hydrogenation was over within about 1 hour. The solution was filtered through a glass sintered funnel with suction and the residue

was washed with ethyl acetate. The clear and colourless filterate and washings were evaporated to dryness under reduced pressure by keeping the flask in cold water. The white crystalline residue obtained was treated with 15 ml. of ether dried over sodium metal and filtered on a glass sintered funnel. The product was washed twice with 10-ml. portions of dry ether. The perfectly white 2-benzyl-4-anisyl-5(4H)-imidazolone melting at 134-136° weighed 0.65 g. (64.6%).

IV: HYDROLYSIS OF SATURATED 2,4-DISUBSTITUTED 5(4H)-IMIDAZOLONES

(a) Acylamino acid amides

1. dl-N-Benzoylphenylalanine amide

In a 100-ml. standard-joint flask a mixture of 1 g. (0.004 mole) of 2-phenyl-4-benzyl-5(4H)-imidazolone and 20 ml. of a sodium hydroxide solution (1 %) was taken and refluxed on a heating mantle. The flask was often shaken till the imidazolone was almost completely dissolved to form a pale yellow solution by the time the boiling began. Within 5 minutes of refluxing benzoylphenylalanine amide began to separate and a lot of the amide separated soon. There was evolution of ammonia due to the hydrolysis of the amide. It was refluxed totally for 15 minutes. The flask with its contents was allowed to cool and the product was filtered on a glass sintered funnel. The filterate was pale yellow. The product was first washed twice with 5-ml. portions of distilled water and then thrice with 5-ml. portions of ether and dried. The yield of white benzoylphenylalanine amide melting at 194-195° was 0. 285 g. (26.6%).

Recrystallisation: Benzoylphenylalanine amide (0.1 g.) was dissolved in chloroform (18 ml.) by heating in a water bath. The solution was filtered, the crystals separated in the

filterate during the filteration were redissolved and the solution was allowed to stand at room temperature overnight. The needle shaped crystals separated were filtered on a Hirsch funnel, washed thrice with 3-ml. portions of distilled ether and dried. The white needle shaped crystals weighed 0.075 g. (75%) and melted at 197.5-198°. The mixed m.p. of this amide with an authentic sample was also 197.5-198°. Mohr and Stroschein (334) reported m.p. 196°. The infra red spectrum of this substance and that of the authentic sample were identical.

Anal. Found: C, 71.20; H, 6.10; N, 10.67

Calc. for $C_{16}H_{16}O_2N_2$: C, 71.62; H, 6.01; N, 10.44

2. <u>dl-N-Benzoylisoleucine amide</u>

A mixture of 2-phenyl-4-sec-butyl-5(4H)-imidazolone (1 g., 0.0046 mole) and 1% solution of sodium hydroxide (30 ml.) was taken in a 100-ml. standard-joint flask and heated under reflux on a wire gauge with shaking. The imidazolone completely dissolved to form a pale yellow solution by the time the refluxing began. Now the shaking of the flask was stopped. After a few minutes of refluxing white benzoylisoleucine amide began to separate in plenty. There was evolution of ammonia gas due to the hydrolysis of amide. After it was refluxed totally for one hour the flask

with its contents was allowed to cool. The product was filtered with suction, washed thrice with 7.5-ml. portions of distilled water and dried in the oven at about 105° for 1 hour. The weight of the white benzoylisoleucine amide melting at 215.5-216.5° was 0.74 g. (68.3%).

Recrystallisation: Benzoylisoleucine amide (0.25 g.) was recrystallised from 35% alcohol (40 ml.). The yield of absolutely white crystals melting at 216-216.5° was 0.19 g. (76%).

Anal. Found: C, 66.91; H, 7.77; N, 11.94

$C_{13}H_{18}O_2N_2$ requires: C, 66.64; H, 7.74; N, 11.96

3. dl-N-Benzoylvaline amide:

In a 100-ml. standard-joint flask a mixture of 1 g. (0.005 mole) of 2-phenyl-4-isopropyl-5(4H)-imidazolone and 30 ml. of sodium hydroxide solution (1%) was taken and heated under reflux on a wire gauze with shaking. The imidazolone readily dissolved to form a pale brown solution. Now the shaking of the flask was stopped. White crystals of benzoylvaline amide began to separate in plenty within about 10 minutes of refluxing. There was evolution of ammonia due to the hydrolysis of the amide. It was refluxed totally for 1 hour. The flask with its contents was allowed to cool and the product was filtered on a glass sintered funnel. The

filterate was pale brown. The product was washed three times with 7.5 ml. portions of water and dried in the oven at 100° for 1 hour. The perfectly white benzoylvaline amide melting at 218-219° weighed 0.51 g. (46.8%).

Recrystallisation: Benzoylvaline amide (0.25 g.) was dissolved in 35% alcohol (25 ml.) and the solution was filtered through a fluted filter paper. The crystals separated from the filterate during the filteration were redissolved and the solution was allowed to stand at room temperature overnight. The white spongy crystals separated were filtered with suction, washed thrice with 3-ml. portions of ether and dried. The yield of absolutely white crystals melting at 219-219.5° was 0.18 g. (72%).

Anal. Found: C, 65.68; H, 7.29; N, 12.70

$C_{12}H_{16}O_2N_2$ requires: C, 65.43; H, 7.32; N, 12.72

4. dl-N-Phenylacetylphenylalanine amide

A mixture of 0.8 g. (0.0030 mole) of 2,4-dibenzyl-5(4H)-imidazolone and 20 ml. of sodium hydroxide solution (1%) was taken in a 100-ml. standard-joint flask and heated under reflux on a heating mantle. Most of the imidazolone dissolved and the phenylacetylphenylalanine amide began to separate by the time the boiling began. A lot of amide separated. After refluxing for 15 minutes, the flask with its contents was allowed to cool. The product was filtered on a glass sintered

funnel, washed first with distilled water and then with ether and dried. The yield of white phenylacetylphenylalanine amide melting at 187-188° was 0.25 g. (29.3%).

Recrystallisation: On recrystallisation of 0.175 g. of phenylacetylphenylalanine amide from dilute alcohol 0.125 g. (71.4%) of absolutely white needle shaped crystals melting at 189-190° was obtained. Erlenmeyer and Kunlin (166) reported melting point 186°.

Anal. Found:	C, 72.02; H, 6.54; N, 10.15
Calc. for $C_{17}H_{18}O_2N_2$:	C, 72.32; H, 6.43; N, 9.92

(b) Acylamino acids

1. dl-N-Benzoylphenylalanine

In a 250-ml. standard-joint flask a mixture of 3 g. (0.012 mole) of 2-phenyl-4-benzyl-5(4H)-imidazolone and 70 ml. of sodium hydroxide solution (0.25 N) was taken and refluxed on a heating mantle for 2 hours. On heating the mixture with shaking the imidazolone readily dissolved to form a pale yellow solution by the time the boiling began. Within about 5 minutes of refluxing benzoylphenylalanine amide began to separate and the solution was full of the amide soon. The flask was occasionally shaken from the time at which the amide began to separate till it was completely dissolved after about 50 minutes. The amide was hydrolysed to benzoylphenylalanine with much evolution of ammonia. After the total

refluxing for 2 hours (even now there was slight evolution of ammonia) the pale yellow solution was allowed to cool. Without filtering to remove the little solid present, carbon dioxide (free from hydrogen chloride) was passed through it, when the unhydrolysed imidazolone precipitated. The solid was removed by filteration when it settled down. The slightly pale yellow filterate was extracted twice with 50-ml. portions of ethyl acetate. The almost colourless solution obtained was acidified with 2.5 ml. of concentrated hydrochloric acid. A lot of benzoylphenylalanine separated. It was allowed to stand at room temperature overnight and filtered on a glass sintered funnel. The product was thoroughly washed twice with 5-ml. portions of distilled water and then twice with 5 ml. portions of ether and dried. The almost white benzoyl-phenylalanine melting at 184-185° weighed 2.21 g. (68.5%).

Recrystallisation: Benzoylphenylalanine (2 g.) was dissolved in glacial acetic acid (8 ml.) by heating to boil and the solution was filtered through a micro glass sintered funnel with suction. The flask was washed by heating with 2 ml. of glacial acetic acid and filtered into the main bulk. The crystals separated from the filterate during the filteration were redissolved and the slightly pale yellow solution was allowed to st nd at room temperature overnight and the crystals separated were filtered on a glass sintered funnel. The

crystals were washed twice with 5-ml. portions of ether and dried. The weight of the white crystals melting at 184.5-185.5° was 1.8 g. (90%). The mixed m.p. of this benzoyl derivative with an authentic sample was also 184.5-185.5°. Lamb and Robson (138) and Ronwin (349) reported melting points 184-185° and 185° respectively. The infra red spectra of this substance and the authentic sample were identical.

Anal. Found: C, 71.68; H, 5.60; N, 5.61

Calc. for $C_{16}H_{15}O_3N$: C, 71.36; H, 5.61; N, 5.20

2. <u>dl-N-Benzoyltyrosine</u>

One gram (0.0037 mole) of 2-phenyl-4-(p-hydroxybenzyl)-5(4H)-imidazolone (containing the platinum catalyst) was dissolved in 18 ml. of sodium hydroxide solution (2%) and filtered into a 100-ml. standard-joint flask. To the pale red brown filterate 18 ml. of distilled water was added and refluxed on a wire gauze for 1.5 hours. No benzoyltyrosine amide separated. There was much evolution of ammonia. After refluxing, the solution was allowed to attain room temperature and the unhydrolysed imidazolone was precipitated by passing carbon dioxide. The solid separated was removed by filteration and the pale yellow filterate was acidified with excess of concentrated hydrochloric acid. Benzoyltyrosine separated along with a little pale yellow material. The flask was placed in the ice chest of the refrigerator for 5 hours and

the product was filtered with suction. The product on crystallisation from 50% acetic acid gave 0.5 g. of slightly pale yellow benzoyltyrosine.

Recrystallisation: The above 0.5 g. of benzoyltyrosine on recrystallisation from glacial acetic acid 0.205 g. (19.4%) of white crystals melting at 190.5-191.5° was obtained. Fischer (129) reported m.p. 191-195°.

Anal. Found: C, 67.71; H, 5.43; N, 5.75

Calc. for $C_{16}H_{15}O_4N$: C, 67.36; H, 5.30; N, 4.91

3. dl-N-Benzoyl-O-methyltyrosine

A mixture of 1 g. (0.0036 mole) of 2-phenyl-4-anisyl-5(4H)-imidazolone and 22 ml. of sodium hydroxide solution (1%) was taken in a 100-ml. standard-joint flask and heated under reflux on a wire gauze for 4 hours. In the beginning the flask was often shaken till the imidazolone was practically completely dissolved to form a pale yellow solution within 1 minute of refluxing. Within 5 minutes of refluxing N-benzoyl-O-methyltyrosine amide began to separate and a lot of it formed soon. The flask was occasionally shaken till the amide was practically completely dissolved after about 3.5 hours. There was much evolution of ammonia due to the hydrolysis of the amide to N-benzoyl-O-methyltyrosine. After the total 4 hours of refluxing the reaction mixture was allowed to cool and hydrogen chloride free carbon dioxide was passed through

it in order to precipitate the unhydrolysed imidazolone. The solid separated was removed by filtering twice through the same gravimetric filter paper. The filterate was extracted twice with 25-ml. portions of ethyl acetate. The slightly pale yellow and clear solution was acidified with 1 ml. of concentrated hydrochloric acid, when an oil separated and solidified within a few minutes. It was placed in the refrigerator overnight, and filtered on a glass sintered funnel. The product was thoroughly washed twice with 3-ml. portions of distilled water and then twice with 3-ml. portions of ether and dried. The weight of the white N-benzoyl-O-methyltyrosine was 0.51 g. (47.8%). The product melted at 176-177°.

Recrystallisation: On recrystallisation from glacial acetic acid by adding ether very good yield of white crystals melting at 176.5-177.5° was obtained. Lamb and Robson (139) Carter and Hinmann (350) reported melting points 173° and 178-179° respectively.

Anal. Found: C, 68.37; H, 5.73; N, 5.14

Calc. for $C_{17}H_{17}O_4N$: C, 68.21; H, 5.73; N, 4.68

4. dl-N-Phenylacetylphenylalanine

A mixture of 1 g. (0.0038 mole) of 2,4-dibenzyl-5(4H)-imidazolone and 24 ml. of sodium hydroxide solution (1%) was taken in a 100-ml. standard-joint flask and heated under

reflux for 2.5 hours with occasional shaking. Most of the imidazolone dissolved and the phenylacetylphenylalanine amide began to separate in plenty by the time the refluxing began. A lot of the amide separated and it gradually dissolved with evolution of ammonia. After refluxing, the reaction mixture was allowed to cool and the little insoluble material present in it was removed by filteration. Practically no solid substance separated on passing carbon dioxide through the pale yellow filterate, which indicated complete hydrolysis of the imidazolone. However, it was filtered and the filterate was acidified with excess of concentrated hydrochloric acid when phenylacetylphenylalanine precipitated. It was placed in the refrigerator overnight and filtered on a Hirsch funnel. The product was washed with water and dried. The yield of almost white phenylacetylphenylalanine melting at 128-130° was 0.8 g. (74.9%).

Recrystallisation: Phenylacetylphenylalanine (0.8 g.) on recrystallisation from benzene absolutely white crystals (0.63 g.) melting at 132.5-133.5° were obtained. Erlenmeyer (351) reported m.p. 126°.

Anal. Found: C, 72.39; H, 6.26; N, 4.97

Calc. for $C_{17}H_{17}O_3N$: C, 72.06; H, 6.05; N, 4.94

5. dl-N-Phenylacetyl-O-methyltyrosine

In a 250-ml. standard-joint flask a mixture of 1.4 g.

(0.0048 mole) of 2-benzyl-4-anisyl-5(4H)-imidazolone and 23.5 ml. of sodium hydroxide solution (1%) was taken and refluxed on a heating mantle for 1.5 hours with occasional shaking. Most of the imidazolone dissolved to form a pale brown solution in the cold itself. N-Phenylacetyl-O-methyltyrosine amide began to separate in plenty by the time the boiling began. There was much frothing up of the amide but it gradually dissolved with evolution of ammonia. After refluxing, the contents of the flask were allowed to cool, when a little white material separated. It was removed by filteration. On passing carbon dioxide through the pale yellow filterate only a little unhydrolysed imidazolone separated. It was removed by filteration and the pale yellow and clear filterate was acidified with excess of concentrated hydrochloric acid. A lot of white N-phenylacetyl-O-methyltyrosine separated. It was placed in the refrigerator overnight and filtered on a glass sintered funnel. The product was thoroughly washed three times with a few ml. portions of distilled water and dried in the oven. The crude N-phenylacetyl-O-methyltyrosine melting at 145-147° weighed 1.04 g. (69.8%).

Recrystallisation: Phenylacetyl-O-methyltyrosine (0.2 g.) was dissolved in glacial acetic acid (1 ml.) and ether (10 ml.) was added to the pale brown solution. It was allowed to stand

at room temperature for 1 hour. The lot of white crystals separated were filtered on a glass sintered funnel, washed with ether and dried. The weight of the absolutely white crystals melting at 154-155° was 0.13 g.

Anal. Found: C, 69.25; H, 6.25; N, 4.30

$C_{18}H_{19}O_4N$ requires: C, 68.99; H, 6.11; N, 4.47

(c) Amino acids

1. dl-Phenylalanine

In a mortar 20 g. (0.063 mole) of hydrated barium hydroxide and 3 g. (0.012 mole) of 2-phenyl-4-benzyl-5(4)-imidazolone were mixed well, the mixture was transferred into a 500-ml. long-necked, standard-joint flask, 50 ml. of distilled water was added to the mixture and refluxed on an asbestosed wire gauze for 7.5 hours with occasional shaking. The flask was often shaken till the boiling began. There was much frothing up of the mixture till the solid materials were almost completely dissolved to form a pale yellow solution within a few minutes of refluxing. There was much evolution of ammonia for the first few hours of refluxing and the pale yellow solution gradually became some what brown. When the heating was stopped there was slight evolution of ammonia.

On the next day the reaction mixture was diluted with 300 ml. of distilled water and the barium was precipitated with 30 ml. of dilute sulphuric acid (1:5). The mixture was

heated in a wat r bath at 50-55° for 15 minutes with occasional shaking. The mixture was then allowed to stand at room temperature. When the tarium sulphate settled down the solution was filtered through a glass sintered funnel by decantation and the residue was washed with a few ml. of distilled water. The clear and practically colourless filtrate and washings were transferred into a 1-l. long-necked flask and concentrated under reduced pressure by heating the flask in a water bath at 50-55° till the volume was reduced to about 75 ml. A lot of white benzoic acid separated. The mixture was cooled and shaken with 75 ml. of ether, when the benzoic acid was completely dissolved. After shaking well in a separating funnel the ether layer was removed. The aqueous layer was extracted twice more with 50-ml. portions of ether. The clear and colourless solution was then concentrated under reduced pressure to about 15 ml. by heating the flask in the water bath at 50-55°. The concentrate was slightly pale yellow. It was slowly treated with liquor ammonia till the pH became 7. (3.6 ml. of liquor ammonia of density 0.988 was required). A lot of white phenylalanine separated. It was placed in the refrigerator overnight and filtered on a glass sintered funnel. The product was first washed thrice with 3-ml. portions of ice-cold distilled water and then thrice with 5-ml. portions of alcohol. It was dried

in the oven at about 85° for 1 hour. The white phenylalanine weighed 1.2 g. (60.6%) and decomposed at 267° (on rapid heating and introducing the substance in the bath at 200°). A second crop of 0.145 g. (7.3%) of phenylalanine was obtained from the filterate and water washings on concentration. The total yield was 1.345 g. (67.9%).

Recrystallisation. Crude phenylalanine (0.9 g.) was dissolved in excess of distilled water and the solution was filtered. The filterate was concentrated on a wire gauze till the crystals just began to form (now the volume was only about 6 ml.) To the hot solution 20 ml. of ethyl alcohol was added and shaken well. A lot of crystals separated soon. When the mixture attained room temperature it was placed in the refrigerator. On the next day the crystals were filtered on a Hirsch funnel and washed thrice with 3-ml. portions of alcohol. The crystals were dried in the oven at 80° for one hour. The absolutely white phenylalanine weighed 0.33 g. (66%). It decomposed at 278° (on rapid heating and introducing the substance in the bath at 200°). The mixed d.p. of this amino acid with an authentic sample was also 278°. Gillespie and Snyder (137) and Albertson and Tullar (253) reported decomposition points 284-288° (corr.) and 275-277° respectively. The infra red spectra of this substance and the authentic sample were identical. p-Toluenesulphonyl

derivative was prepared and it melted at 134-135°. The melting point recorded by McChesney (352) is also 134-135°.

Anal. Found: C, 65.53; H, 6.56; N, 8.84

Calc. for $C_9H_{11}O_2N$: C, 65.44; H, 6.71; N, 8.48

2. dl-O-Methyltyrosine

2-Phenyl-4-anisyl-5(4H)-imidazolone (1 g., 0.0036 mole) was mixed with hydrated barium hydroxide (6 g., 0.019 mole) in a mortar, the mixture was taken in a 250-ml. long-necked, standard-joint flask, distilled water (15 ml.) was added to it and heated on an asbestosed wire gauze under reflux for 7.5 hours with occasional shaking. On heating the mixture with shaking the barium hydroxide and most of the imidazolone dissolved to form a pale yellow solution by the time the boiling began. There was a lot of evolution of ammonia during the first few hours of refluxing. At the end of the total 7.5 hours of refluxing there was a little evolution of ammonia. When the reaction mixture attained room temperature it was diluted with 100 ml. of distilled water. The barium was precipitated with 10 ml. of dilute sulphuric acid (1:5). The mixture was heated on a water bath at about 55° for 15 minutes with occasional shaking to make the barium sulphate granular. The mixture was allowed to stand at room temperature till the barium sulphate settled down. The solution was filtered through a glass sintered funnel by decantation and

the residue was washed with a few ml. of distilled water. On the next day the slightly pale yellow filterate and washings were concentrated to about 30 ml. under reduced pressure by heating the flask in a water bath at 50-55°. A lot of benzoic acid separated. The benzoic acid was removed by extracting the mixture thrice with 25-ml. portions of ether. The aqueous solutions was concentrated to about 15 ml. under reduced pressure by heating the flask in the water bath at 50-55°. The concentrate was treated slowly with liquor ammonia till the pH became 7. (1.4 ml. of liquour ammonia of density 0.888 was required). A lot of O-methyltyrosine separated. The flask was placed in the refrigerator overnight. The product was filtered on a glass sintered funnel, washed twice with 3-ml. portions of distilled water and then thrice with 3-ml. portions of alcohol. It was dried in the oven at about 90° for 1 hour. The yield of white O-methyltyrosine was 0.37 g. (53.1%). It decomposed at 275° (on rapid heating and introducing the substance in the bath at 200°). On concentrating the combined filterate and water washings a second crop of 0.04 g. (5.7%) of O-methyltyrosine decomposing at 268° was obtained. So the total yield was 0.41 g. (58.9%).

Recrystallisation: O-methyl-tyrosine (0.2 g.) was dissolved in excess of water and the solution was filtered through a fluted filter paper. The clear and colourless filterate was

concentrated on a wire gauze to about 5 ml. when the crystals began to form. To the hot solution 10 ml. of alcohol was added and shaken well. A lot of crystals separated by the time it attained the room temperature. After cooling in the refrigerator overnight the crystals were filtered on a Hirsch funnel and washed thrice with 2-ml. portions of alcohol. It was dried in the oven at about 80° for 1 hour. The weight of the absolutely white crystals of O-methyltyrosine was 0.155 g. (77.5%). It decomposed at 275° (on rapid heating and introducing the substance in the bath at 200°). Dakin (328) and Feofilaktov and coworkers (208) reported decomposition points 295° and 262° respectively. The infra red spectra of this amino acid and an authentic sample were identical.

Anal. Found: C, 61.53; H, 6.49; N, 7.08

Calc. for $C_{10}H_{13}O_3N$: C, 61.52; H, 6.71; N, 7.18

3. <u>dl-Valine</u>

One gram (0.005 mole) of 2-phenyl-4-isopropyl-5(4H)-imidazolone and 8 g. (0.025 mole) of hydrated barium hydroxide were mixed well in a mortar, the mixture was taken in a 250-ml. standard-joint flask, 20 ml. of distilled water was added and refluxed on an asbestosed wire gauze for 7.5 hours with occasional shaking. There was much frothing of the reaction mixture and plenty of evolution of ammonia for the first few hours of refluxing. There was only a little evolution

of ammonia at the end of the refluxing. The reaction mixture was allowed to cool down, diluted with 100 ml. of distilled water and the barium was precipitated by adding 13 ml. of dilute sulphuric acid (1:5). The mixture was heated with occasional shaking in a water bath at about 55° for 15 minutes in order to make the barium sulphate granular. The precipitate was allowed to settle down and the solution was filtered through a glass sintered funnel by decantation. The residue was washed with a few ml. of distilled water. The clear and colourless filterate and washings were concentrated to about 40 ml. under diminished pressure by heating the flask in a water bath at 50-55°. By this time a lot of benzoic acid separated. The mixture was extracted thrice with 30-ml. portions of ether to remove the benzoic acid. The aqueous solution was then treated with excess of barium hydroxide solution to precipitate the sulphate ions and the mixture was heated in the water bath at 50-55° for 15 minutes with occasional shaking. Hydrogen chloride free carbon dioxide was passed through the mixture in cold to precipitate the excess of barium as barium carbonate. The mixture was again heated in the water bath at about 55° for 15 minutes with occasional shaking to make the precipitates granular. When the precipitates settle down the solution was filtered through a glass sintered funnel by decantation and the residue was

washed with a little distilled water. The combined filterate and washings were evaporated to dryness under reduced pressure by heating the flask in a water bath at 50-55°. The white residue was treated with 20 ml. of alcohol and filtered on a Hirsch funnel. It was washed twice with 5-ml. portions of alcohol. The weight of the white product was 0.325 g.

Recrystallisation: The above 0.325 g. product was dissolved in 3 ml. of distilled water and the solution was filtered. The clear and colourless filterate was concentrated under reduced pressure to about 1.5 ml. by heating the flask in a water bath at 60°. To this 5 ml. of ethyl alcohol was added. Fine crystals began to separate soon. The flask was placed in the refrigerator overnight, the crystals were filtered on a Hirsch funnel and washed twice with 1.5-ml. portions of alcohol and dried. The valine decomposed at 290-292° and weighed 0.185 g. (31.9%). After a further crystallisation from the same solvent it decomposed at 305°. Marvel (12) and Feofilaktov and Zaitsev (207) reported decomposition points 280-282° and 305-306° respectively. The infra red spectra of this substance and an authentic sample of valine were identical.

Anal. Found:	C, 51.38; H, 9.25; N, 12.05
Calc. for $C_5H_{11}O_2N$:	C, 51.26; H, 9.46; N, 11.96

V: OTHER SYNTHESES

1. 2-Phenyl-4-benzylidene-5(4H)-imidazolone

2-Phenyl-4-benzylidene-5(4H)-imidazolone was prepared starting with 2-phenyl-4-benzylidene-5-oxazolone essentially according to the method of Erlenmeyer (299, 300).

(a) α-Benzoylaminocinnamic acid amide: In a 500-ml. Erlenmeyer flask a mixture of 37 g. (0.15 mole) of 2-phenyl-4-benzylidene-5-oxazolone and 215 ml. of a saturated solution of ammonia in absolute ethyl alcohol was taken, the flask was corked and shaken. Within 10 minutes the oxazolone was completely dissolved to form a pale yellow solution and white crystals of α-benzoylaminocinnamic acid amide began to separate. Now the solution was added to 500 ml. of distilled water, when a lot of white amide precipitated. On the next day it was filtered on a Buchner funnel and washed with distilled water till the washings became colourless. After drying in the oven at 100° the white product weighed 34.2 g. (86.5%). It melted at 162-163°.

(b) 2-Phenyl-4-benzylidene-5(4H)-imidazolone: A mixture of 33.4 g. (0.125 mole) of powdered α-benzoylaminocinnamic acid amide and 700 ml. of sodium hydroxide solution (1.5%) was taken in a 1-l. conical flask and heated on a steam bath with occasional shaking. Within 20 minutes most of the amide

dissolved to form a red solution and yellow 2-phenyl-4-benzylidene-5(4H)-imidazolone began to separate. It was heated for 70 minutes more, when there was no more separation of the imidazolone. When the reaction mixture attained room temperature it was placed in the refrigerator overnight. The product was filtered off and washed with distilled water. Then it was transferred into a conical flask, heated with 150 ml. of alcohol and again filtered off. The crystals were washed twice with alcohol and dried in the oven at 80°. The yield of yellow crystalline 2-phenyl-4-benzylidene-5(4H)-imidazolone melting at 272-273° was 28.7 g. (92%).

Recrystallisation: 2-Phenyl-4-benzylidene-5(4H)-imidazolone (0.5 g.) was recrystallised from amylacetate (45 ml.). The yellow crystals melted at 273-274°.

2. 2-Phenyl-4-benzyl-5(4H)-imidazolone:

2-Phenyl-4-benzyl-5(4H)-imidazolone was prepared according to the method employed by Cornforth and Huang (305) in the synthesis of 2-phenyl-4-methyl-5(4H)-imidazolone. Phenylalanine ethyl ester hydrochloride was prepared essentially according to the method of Curtius and Muller (353) and converted into the free ester required for the synthesis of the imidazolone, using the method of Fischer (338,339).

(a) Phenylalanine ethyl ester hydrochloride: A mixture of 13.5 g. (0.082 mole) of phenylalanine and 200 ml. of absolute ethyl alcohol was saturated with dry hydrogen chloride gas (dried by bubbling through concentrated sulphuric acid and passing over phosphorous pentoxide), when the phenylalanine dissolved to form a red brown solution. The solution was concentrated to about 35 ml. under reduced pressure. To this 150 ml. of absolute alcohol was added and again saturated with dry hydrogen chloride gas. It was again concentrated under reduced pressure to about 40 ml. The concentrate was transferred into a conical flask and cooled in the refrigerator. About 200 ml. of ether dried over sodium metal was added to it and again placed in the refrigerator. After about 30 minutes phenylalanine ethyl ester hydrochloride began to separate. The crystals separated were filtered after two days, washed with dry ether and dried. The yield of white phenylalanine ethyl ester hydrochloride was 16.5 g. (87.9%). The product melted at 130-131°.

(b) Phenylalanine ethyl ester: Ten grams (0.044 mole) of phenylalanine ethyl ester hydrochloride was dissolved in 11 ml. of distilled water, 30 ml. of ether was added to it and the mixture was cooled in ice. It was slowly neutralised with 5.5 ml. of ice-cold sodium hydroxide solution (40 %).

The mixture was transferred into a separating funnel, shaken well and the ether layer was collected in a conical flask. To the aqueous layer 20 ml. of ether was added and saturated with potassium carbonate by keeping the flask in the ice bath. The ether layer was collected along with the main bulk after shaking in the separating funnel. The aqueous layer was once again extracted with 20 ml. of ether. The combined ether extracts were treated with anhydrous potassium carbonate by keeping the flask in the ice bath. It was placed in the refrigerator for 6 hours, filtered by decantation and washed the residue three times with ether dried over sodium metal. The ether was completely evaporated away under reduced pressure by shaking the flask in water. The clear and colourless phenylalanine ester weighed 7.7 g. (91.6%).

(c) <u>2-Phenyl-4-benzyl-5(4H)-imidazolone</u>: Phenylalanine ethyl ester (6 ml., 0.033 mole) and benzimidic acid ethyl ester (5 ml., 0.034 mole) were mixed well in a dry 100-ml. Erlenmeyer flask, tightly closed and the mixture was allowed to stand at room temperature (20°) for 14.5 hours. The mixture was completely solidified into a pale yellow mass. It was treated with 20 ml. of ether dried over sodium metal, and filtered on a glass sintered funnel. The filterate was pale yellow. The product was washed three times with 10-ml. portions of dry ether and dried by suction. The yield of pale

yellow 2-phenyl-4-benzyl-5(4H)-imidazolone was 4.88 g. (59%). It melted at 168-169° to a clear and pale yellow liquid on rapid heating (the rise of temperature was 13° per minute at about the m.p.).

Recrystallisation: 2-Phenyl-4-benzyl-5(4H)-imidazolone (0.5 g.) was dissolved in distilled benzene (20 ml.) by heating with shaking in a water bath at about 73° for three minutes. The solution was filtered into 2 0 ml. of petroleum ether (b.p, 60-80°). The crystals separated in the petroleum ether during the filteration. The flask was allowed to stand at room temperature for 4.5 hours and the crystals were filtered on a Hirsch funnel. The crystals were washed thrice with 3-ml. portions of distilled ether and dried by suction. The slightly pale yellow crystals melted at 168-169° to a clear and pale yellow liquid on rapid heating (the rise of temperature was 13° per minute at about the m.p.).

Anal. Found: C, 76.79; H, 5.42; N, 11.17

Calc. for $C_{16}H_{14}ON_2$: C, 76.78; H, 5.64; N, 11.19

3. Benzoylphenylalanine amide

Essentially according to the method of Mohr and Stroschein (334) 2-phenyl-4-benzyl-5-oxazolone was prepared and converted into benzoylphenylalanine amide.

A mixture of benzoylphenylalanine (1 g.,0.0037 mole) and acetic anhydride (10 ml.) was taken in a 100-ml. round-bottomed

flask fitted with an air condenser and heated on a steam bath for 0.5 hour. When the colourless solution obtained was concentrated under reduced pressure 1 ml. of a syrupy residue left. It was dissolved in petroleum ether, 3 ml. of liquor ammonia was added to it and shaken, when white benzoylphenylalanine amide separated. More petroleum ether was added for the complete precipitation of the amide. After keeping for some time it was filtered and washed with petroleum ether.

Recrystallisation: Benzoylphenylalanine amide (0.2 g.) was recrystallised from chloroform (35 ml.). The white needle shaped crystals melted at 197.5-198°.

4. Hydrolysis of benzoylphenylalanine amide (prepared from imidazolone)

A mixture of benzoylphenylalanine amide (0.3 g.,0.00112 mole) and 8 ml. of sodium hydroxide solution (1%) was taken in 50-ml. standard-joint flask and refluxed for two hours with occasional shaking. The amide was completely dissolved within 1.5 hours of refluxing. There was much evolution of ammonia due to the hydrolysis of the amide to benzoylphenylalanine. After the refluxing, the solution was allowed to cool and carbon dioxide (free from hydrogen chloride) was passed through it. The little turbidity formed was removed by filteration and the filterate was extracted twice with 10-ml. portions of ethyl acetate. The practically colourless

solution was acidified with 0.5 ml. of concentrated hydrochloric acid, when benzoylphenylalanine separated. After keeping the flask at room temperature overnight the product was filtered on a Hirsch funnel. It was thoroughly washed twice with 3-ml. portions of distilled water and then twice with 3-ml. portions of ether and dried. The white product weighed 0.22 g. (73.1%) and melted at 184-185.5°.

5. A white product melting at 246°

Method I: Two grams (0.0081 mole) of crude 2-phenyl-4-benzylidene-5(4H)-imidazolone (powdered) was hydrogenated in a Tower's semi-micro hydrogenation apparatus at room temperature and under atmospheric pressure using 0.75 g. of palladium on barium sulphate catalyst in the presence of 150 ml. of ethyl alcohol as solvent. The rate of absorption of hydrogen was uniform and the substance absorbed one molecular proportion of the gas. On the next day the solution was filtered and the pale yellow filterate was concentrated to a few ml. under reduced pressure from a hot water bath. A lot of white substance separated. It was filtered, washed with alcohol and dried. The white product weighed 0.8 g. and melted at 242° with decomposition.

Recrystallisation: On recrystallisation from alcohol (in which the crude product was only partly soluble) absolutely white needle like spongy crystals melting at 246° with

decomposition was obtained.

Method II: One gram of 2-phenyl-4-benzyl-5(4H)-imidazolone (m.p. 168-169°) was dissolved in 10 ml. of ethyl alcohol, the pale yellow solution was filtered and allowed to stand at room temperature. By the next morning some white substance deposited on the side of the flask. On further keeping more and more white substance formed. After 7 days the product was filtered off, washed with alcohol and dried. The white product melting at 242° with decomposition weighed 0.3 g.

Recrystallisation: As in the previous case the crude product on recrystallisation from alcohol (in which it was only partly soluble) absolutely white needle like spongy crystals melting at 246° with decomposition was obtained. The mixed melting point of this product with that obtained by method I was also 246°.

6. Reduction of 2-phenyl-4-benzyl-5(4H)-imidazolone

2-Phenyl-4-benzyl-5(4H)-imidazolone (0.45 g., 0.0018 mole) and ethyl alcohol (50 ml.) were taken in a 250-ml. three-necked flask fitted with a mechanical stirrer and a dropping funnel. Sodium amalgam prepared by taking 1 g. of sodium and 40 g. of mercury was added to it in small portions through the third neck. The mixture was being stirred after the third neck was loosely corked and 3 ml. of glacial acetic acid was added to the mixture periodically in a course of

one hour. Then the mecury was removed by filteration, the pale yellow filterate was evaporated to dryness under reduced pressure by keeping the flask in cold water. The residue was treated with water and filtered off. The product became white on treating with ether.

Recrystallisation: On recrystallisation from xylene (using carbon) colourless crystals of 2-phenyl-4-benzyl-5-imidazolidone melting at 145-146° was obtained. The mixed m.p. of this substance with an authentic sample was also 145-146°. The melting point reported by Granacher and Gulbas (324) is also 145-146°.

7. Reduction of the white product melting at 246°

A mixture of 0.55 g. of the white product (recrystallised) melting at 246° and 100 ml. of ethyl alcohol was taken in a 500-ml. three-necked flask fitted with a mechanical stirrer, reflux condenser and a dropping funnel. After heating the mixture to boil sodium amalgam prepared by taking 1 g. of sodium and 45 g. of mercury was added to it in small portions through the condenser. The mixture was being stirred and about 2.5 ml. of glacial acetic acid was added periodically in a course of one hour. The stirring was continued for 0.5 hour and the solution was filtered hot. The pale yellow filterate was evaporated to dryness under reduced pressure

by keeping the flask in cold water. The residue was treated with water and filtered off. The product became white on treating with ether. It was filtered, off washed with ether and dried. The product weighed 0.15 g. and melted at 138-139°.

Recrystallisation: On recrystallisation from xylene (using carbon) colourless crystals melting at 145-146° was obtained. The mixed melting point of this product with an authentic sample of 2-phenyl-4-benzyl-5-imidazolidone was also 145-146°. The melting point of 2-phenyl-4-benzyl-5-imidazolidone reported by Cranacher and Gulbas (324) is also 145-146°.

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